Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Post-COVID syndrome: the aftershock of SARS-CoV-2

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Introduction

Significant time has passed since the coronavirus disease of 2019 (COVID-19) pandemic outbreak, which led to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in hundreds of millions of individuals all around the globe. An accumulation of evidence during the pandemic raised awareness of an association between the SARS-CoV-2 and autoimmunity (Dotan et al., 2021 Apr). SARS-CoV-2 infected patients have a high presence of various autoantibodies (Dotan et al., 2021 Apr). Moreover, numerous cases of new-onset of autoimmune-related disorders have been documented following infection, including both organ-specific and systemic autoimmune diseases (Dotan et al., 2021 Apr).

Recent studies analyzing recovered COVID-19 patients demonstrate a broad spectrum of persistent and systemic symptoms, which introduced the novel terms, “post-COVID syndrome," "long COVID," and "chronic COVID-19" (Alwan, 2020 Aug 11). This new disorder had led to the understanding that the absence of SARS-CoV-2 following COVID-19 does not necessarily mean full recovery (Alwan, 2020 Aug 11).

Follow-up studies of COVID-19 patients indicate that 50-80% of symptomatic COVID-19 patients who recovered report non-specific symptoms, most commonly fatigue, headache, dyspnea, anosmia, and memory complaints (Carfì, Bernabei, and Landi, 2020 Aug 11, Puntmann et al., 2020 Nov 1, Mahmud et al., 2021 Apr 8). An Italian study that examined patients after a average of 60 days from the first COVID-19 symptom onset, found that only 12.6% of the patients completely recovered; 55% had three or more symptoms and a worsened quality of life was observed among 44% of patients (Carfì, Bernabei, and Landi, 2020 Aug 11). Intriguingly, a systematic review and meta-analysis reported more than 50 possible long-term effects of the SAR-CoV-2 infection (Lopez-Leon et al., 2021 Aug 9). The chronic phase of COVID-19 is also presented in objective findings. For example, a study conducted in Germany found that 78% of recently recovered symptomatic COVID-19 patients had at least one chronic symptom; the most common abnormality was myocardial infarction or inflammation (60%) (Puntmann et al., 2020 Nov 1).

In this issue of the journal, Bertin D et al. document a case of post-COVID syndrome with a one-year follow-up. This case describes persistent anti-cardiolipin IgG autoantibodies and eosinopenia with ongoing neurologic symptoms, demonstrating the potential long-term Pathogenicity of SARS-CoV-2. Anti-cardiolipin autoantibodies and eosinopenia were recognized as independent factors associated with COVID-19 severity, indicating their active involvement in the progression of the disease (Lindsley, Schwartz, and Rothenberg, 2020 Jul 1, Jizzini, Shah, and Zhou, 2020 Dec). Additional studies that included follow-up on recovered COVID-19 patients describe similar findings: patients report respiratory, neurologic, and non-specific symptoms, accompanied by the presence of autoantibodies (Lopez-Leon et al., 2021 Aug 9). Of some interest, in a one-year prospective cohort study, neurocognitive symptom fre-

Abbreviations: SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease of 2019.

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quency was found significantly higher in patients with an ANA titer of ≥1:160 in comparison to <1:160 at 12 months post–COVID-19 symptom onset (Seeßle et al., 2021). It should be emphasized that the development of autoantibodies, which appears to be expected following symptomatic SARS-CoV-2 infection, could act as the preclinical stage of many autoimmune diseases. Thus, the long-term autoimmune implications of SARS-CoV-2 could be severe.

Involvement of autonomic nervous system dysfunction in post-COVID syndrome

Many viruses are known to contribute to autoimmunity in genetically pre-dispositioned individuals, such as those with human leukocyte antigen B27 (Shoenfeld et al., 2008 Jan). SARS-CoV-2 has been associated with numerous autoantibodies (Dotan et al., 2021 Apr), some of which are believed to be the basis of the severe forms of COVID-19 (Khamsi, 2021 Jan 19). Furthermore, these autoantibodies, along with others, could lead to the multi-organ involvement of post-COVID syndrome, manifesting as broad and non-specific symptoms (Lopez-Leon et al., 2021 Aug 9). Autoantibodies against the autonomic nervous system are believed to be an incremental part of the post-COVID syndrome etiology.

A study examining functionally active autoantibodies against the autonomic nervous system in post-COVID syndrome patients found that all subjects had between two to seven different receptor agonists antibodies, such as β2-adrenoceptor, α1-adrenoceptor, and angiotensin II receptor type 1 receptor (Wallukat et al., 2021 Jan 1). Functionally active autoantibodies such as these were present in several neurological and cardiac disorders, which might clarify the onset of neurological and cardiovascular symptoms of the post-COVID syndrome (Wallukat et al., 2021 Jan 1).

Post-COVID patients commonly have a clinical presentation similar to the encephalomyelitis/chronic fatigue syndrome (ME/CFS): severe fatigue, sleep disorders, cognitive impairments, and different manifestations of autonomic dysfunction exacerbated in physical exercise (Lopez-Leon et al., 2021 Aug 9, Huang et al., 2021 Jan 16, Wostyn, 2021 Jan, Bornstein et al., 2021 Jun 17). ME/CFS has an autoimmune etiology, demonstrated by high titers of autoantibodies against autonomic receptors, such as beta-adrenergic and muscarinic receptors (Rasa et al., 2018 Oct 1, Loebel et al., 2016 Feb 1). These autoantibodies, similar to those found in patients with post-COVID symptoms, lead to non-specific symptoms due to autonomic nervous system dysregulation. In addition to ME/CFS, many features of the post-COVID syndrome are shared with fibromyalgia patients. It has been shown that 189/616 (30.7%) of COVID-19 recovered patients satisfied the American College of Rheumatology criteria for fibromyalgia, 43.4% of which were men (Ursini et al., 2021 Aug 1).

Therapeutic options and vaccination

ME/CFS and fibromyalgia have solid evidence of dysregulated immune involvement (Rasa et al., 2018 Oct 1, Loebel et al., 2016 Feb 1, Rodriguez-Pintó et al., 2014 Oct). Moreover, current studies suggest that immunosuppression, such as monoclonal anti-CD20 antibody and cyclophosphamide, may benefit patients suffering from ME/CFS (Tölle et al., 2020 Aug, Rekeland et al., 2020). Such immunosuppressive therapeutic options can assist in the depletion of B cells, thus reducing the functionally active autoantibodies linked to autonomic dysfunction. Beneficial effects have also been demonstrated by the use of anti-ß2 adrenergic receptor-binding immunoadsorption (Scheibenbogen et al., 2018). It should be emphasized that such treatment can diminish other pathogenic antibodies that the medical community has not yet recognized. Due to the possible involvement of autoantibodies against the autonomic nervous system in the post-COVID syndrome, similar immunosuppressive options in these patients may be effective; therefore they should be investigated.

Many studies had shown that the majority of individuals infected by SARS-CoV-2 are asymptomatic or experience merely mild symptoms (Salzberger et al., 2021 Apr, Gao et al., 2021 Feb). While the frequency of post-COVID syndrome in such individuals is still uncertain, it seems to be much lower in comparison to patients which were symptomatic in the acute phase of COVID-19 (Seeßle et al., 2021). Thus, avoiding COVID-19 with SARS-CoV-2 vaccination could markedly assist in preventing long-term symptoms of COVID-19, lower the prevalence of post-COVID syndrome and help overcome the pandemic. Nonetheless, even with the ongoing mass vaccination programs, the COVID-19 pandemic will leave its mark.

Conclusion

Due to the accumulating evidence of persistent post-infection symptoms reported by numerous recovered patients, the focus of the medical and research communities might well shift focus from the acute phase of COVID-19 to the chronic manifestations of the SARS-CoV-2 infection, now referred to as “post-COVID syndrome." Post-COVID syndrome presents as a non-specific symptomatology, most commonly fatigue, headache, dyspnea, anosmia, and memory complaint, which is suspiciously similar to the infection-induced myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and fibromyalgia (Bornstein et al., 2021 Jun 17, Ursini et al., 2021 Aug 1). Considering that current studies suggest an involvement of immune-related dysfunction in the development of post-COVID syndrome, immunosuppressive therapeutic options could be beneficial in parallel with massive SARS-CoV-2 vaccination of the populace (Bornstein et al., 2021 Jun 17, Tölle et al., 2020 Aug, Rekeland et al., 2020).

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