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LETTER

People with a connective tissue disorder may be especially vulnerable to the endothelial damage that characterizes long COVID due to the fragility of their vasculature and slow wound healing

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Abstract
A growing body of evidence documents the central role that endothelial damage plays in the pathophysiology of long COVID. But it remains unclear why only certain people get Long COVID and why recovery times are so long for many affected individuals. One potential explanation is that some forms of long COVID are experienced disproportionately by people with a connective tissue disorder who are more vulnerable than others to incurring serious damage to the endothelium and the vascular extracellular matrix from the inflammatory processes triggered by COVID-19 and much slower to heal. Further research is needed to explore this hypothesis.

Keywords Long COVID · Post-COVID syndrome · Postacute sequelae of SARS-CoV-2 · Connective tissue disorders

Dear Editor,

I am writing in response to a recent paper published in *Angiogenesis* by Wu et al. [1] As this paper effectively documents, endothelial damage appears to play a central role in the pathophysiology of long COVID. Important questions remain, however. Why do only a fraction of those who experience a severe COVID-19 infection go on to develop long COVID? Why do people who experience only mild initial infections nevertheless develop long COVID? Why do some people recover from long COVID, while others do not? And why does recovery vary substantially from person to person, with many people experiencing long COVID as a condition lasting for longer than a year?

One possible explanation is that some forms of long COVID are experienced disproportionately by people with a connective tissue disorder who are more vulnerable than others to incurring serious damage to the endothelium and the vascular extracellular matrix from the inflammatory processes triggered by COVID-19 and much slower to heal. Among other connective tissue disorders, Ehlers–Danlos syndrome [EDS], Marfan syndrome, Neurofibromatosis Type 1, and Loeys–Dietz syndrome have been associated with neurovascular complications related to a fragile vasculature [2]. While the vascular risks of vascular EDS are well recognized, people with non-vascular forms of EDS, including the more common classical and hypermobile types, are also susceptible to vascular complications [3, 4]. Many autoimmune connective tissue disorders, including rheumatoid arthritis, lupus and scleroderma, are also characterized by vascular complications and slow wound healing [5].

The inflammatory cascade of a severe acute COVID-19 infection may cause serious vascular damage in people with and without a connective tissue disorder, but I hypothesize that a mild initial infection is much more likely to cause serious long-lasting vascular damage in people with a connective tissue disorder. I further hypothesize that the slow wound healing experienced by people with EDS and other connective tissue disorders [2] contributes to the extended duration of some forms of long COVID and that differences in recovery times may be associated both with the severity of the initial vascular injury and the severity of the subject's connective tissue disorder. People with a connective tissue disorder may also be more likely than others to experience ongoing injuries to the endothelium as a result of persistent inflammation and immune dysregulation.

This hypothesis is supported by a study of 229 individuals with the related condition of myalgic encephalomyelitis/chronic fatigue syndrome, which found that half had

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generalized joint hypermobility, a marker of connective tissue disorders, based on thresholds tied to the 5th percentile of a very large sample stratified by age and gender [6].

Research on the prevalence of connective tissue disorders among those with different forms of long COVID would be helpful in evaluating this hypothesis. Since connective tissue disorders are often underdiagnosed, it will be important to supplement medical records with other data. This could include measures of hypermobility, such as the Beighton score and the 5PQ hypermobility questionnaire, and genetic testing to identify other known markers of a connective tissue disorder. Information about pre-COVID symptoms could help researchers distinguish between symptomatic and asymptomatic hypermobility. Measures of intracranial hypertension and craniocervical instability, such as those employed by Bragee et al. [6], may also be useful as ways to identify neurological features associated with connective tissue disorders that may contribute independently to the symptoms experienced by people with long COVID.

It is presently unclear whether the vascular damage associated with long COVID is caused by one or more major inflammatory events that is/are very slow to heal (perhaps due to a connective tissue disorder) or by ongoing/daily injuries associated with persistent inflammation, or some combination. To the extent that the vascular damage experienced by people with some forms of long COVID stems from one or more major inflammatory events, efforts to speed up wound healing and to prevent relapsing inflammatory events (such as injury from ischemia-reperfusion or mast cell activation) could help to accelerate recovery.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The author has no competing interests to declare that are relevant to the content of this article.

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