Long COVID leaves telltale traces in the blood, finds new study

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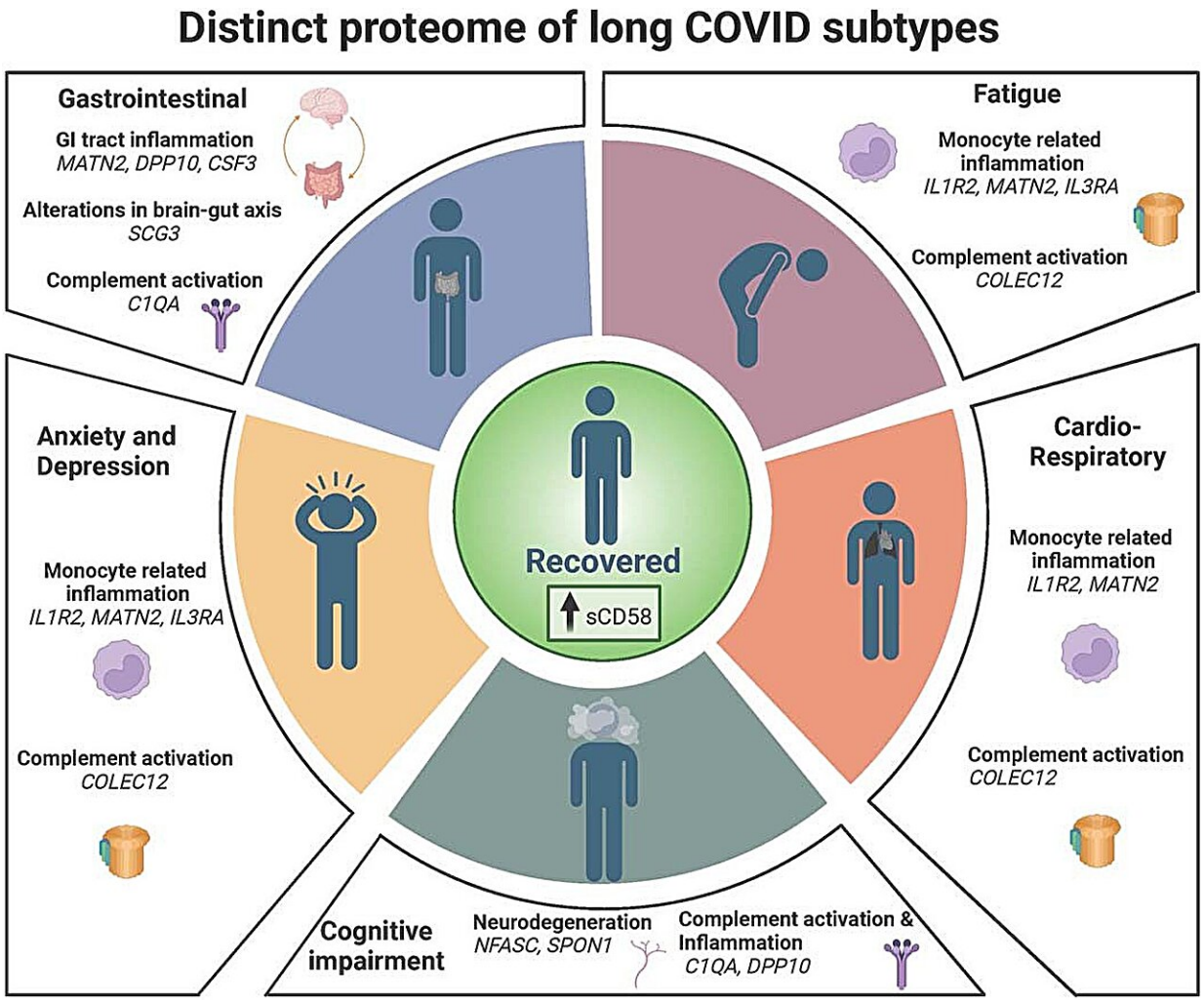

Graphical abstract. Credit: *Nature Immunology* (2024). DOI: 10.1038/s41590-024-01778-0

Findings from the largest UK study of patients hospitalized with SARS-CoV-2 infection show that long COVID leads to ongoing inflammation which can be detected in the blood.

In an analysis of more than 650 people who had been hospitalized with severe COVID-19, patients with prolonged symptoms showed evidence of immune system activation.

The exact pattern of this activation varied depending on the sort of symptoms that they predominantly had—for example, mainly fatigue or cognitive impairment.

The research, led by Imperial College London, suggests that existing drugs which modulate the body's immune system could be helpful in treating long COVID and should be investigated in future clinical trials.

The study, published in the journal *Nature Immunology*, is the latest research from two collaborative UK-wide consortia, PHOSP-COVID and ISARIC-4C.

These involve scientists and clinicians from Imperial alongside collaborators from the Universities of Leicester, Edinburgh, and Liverpool, among others.

Professor Peter Openshaw, from Imperial's National Heart & Lung Institute and an ISARIC-4C lead investigator, said, "With one in ten SARS-CoV-2 infections leading to long COVID and an estimated 65 million people around the world suffering from ongoing symptoms, we urgently need more research to understand this condition. At the moment, it's very hard to diagnose and treat."

"This study, which includes detailed clinical data on symptoms and a raft of inflammatory blood plasma markers, is an important step forward and

provides crucial insights into what causes long COVID."

Runaway inflammation

In the latest study, researchers included a total of 426 people who were experiencing symptoms consistent with long-term COVID-19 and had been admitted to hospital with COVID-19 infection at least six months prior to the study.

They were compared with 233 people who were also hospitalized for COVID-19 but who had fully recovered. The researchers took samples of blood plasma and measured a total of 368 proteins known to be involved in inflammation and immune system modulation.

They found that relative to patients who had fully recovered, those with long COVID showed a pattern of immune system activation, indicating inflammation of myeloid cells and activation of a family of immune system proteins called the complement system.

Myeloid cells are formed in the bone marrow and produce various types of white blood cells that circulate in the blood and migrate into organs and tissues, where they respond to damage and infection.

The complement system consists of a cascade of linked proteins that are activated in response to infection or tissue damage. Notably, overactivation of the complement system is known to be associated with many autoimmune and inflammatory conditions.

Dr. Felicity Liew, from Imperial's National Heart & Lung Institute, said, "Our findings indicate that complement activation and myeloid inflammation could be a common feature of long COVID after hospitalization, regardless of symptom type."

"It is unusual to find evidence of ongoing complement activation several months after acute infection has resolved, suggesting that long COVID symptoms are a result of active inflammation."

"However, we can't be sure that this is applicable to all types of long COVID, especially if symptoms occur after non-hospitalized infection."

Sub-types of long COVID

The researchers were also able to obtain comprehensive information about the range of symptoms that patients were experiencing and which ones were most common.

They found that certain groups of symptoms appeared to be associated with specific proteins. For example, people with gastrointestinal symptoms had increased levels of a marker called SCG3, which has previously been linked to impaired communication between the gut and the brain.

Overall, there were five overlapping subtypes of long-term COVID with different immune signatures, despite some commonalities, namely fatigue, cognitive impairment, anxiety and depression, cardiorespiratory, and gastrointestinal.

The researchers stress, however, that these groups are not mutually exclusive, and people can fall between groups depending on their symptoms.

Nevertheless, these long COVID subtypes seem to represent clear biological mechanisms of disease and highlight that different symptoms may have different underlying causes. The researchers suggest this could be useful in designing clinical trials, especially for treatments that target immune responses and inflammation.

One such treatment could include drugs called IL-1 antagonists, such as anakinra, which is commonly used to treat rheumatoid arthritis, as well as another drug class called JAK inhibitors, used to treat some types of cancers and severe forms of rheumatoid arthritis. Both drug types work by targeting components of the immune system that might be activated in long COVID.

The researchers highlight that one limitation of their study was that it only included people who had severe SARS-CoV-2 infections and who were hospitalized as a result. Yet a sizeable proportion of people who develop long COVID in the wider population only report mild initial SARS-CoV-2 infection, and it's unclear if the same immune mechanisms are at work.

Professor Openshaw concludes, "This work provides strong evidence that long COVID is caused by post-viral inflammation but shows layers of complexity."

"We hope that our work opens the way to the development of specific tests and treatments for the various types of long COVID and believe that a 'one size fits all' approach to treatment may not work."

"COVID-19 will continue to have far-reaching effects long after the initial infection has passed, impacting many lives. Understanding what's happening in the body, and how the immune system responds, is key to helping those affected."

More information: Peter Openshaw, Large-scale phenotyping of patients with long COVID post-hospitalization reveals mechanistic subtypes of disease, *Nature Immunology* (2024). DOI: 10.1038/s41590-024-01778-0.

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