Telltale amino acid deficiencies may hold the key to new treatments for long COVID, say researchers

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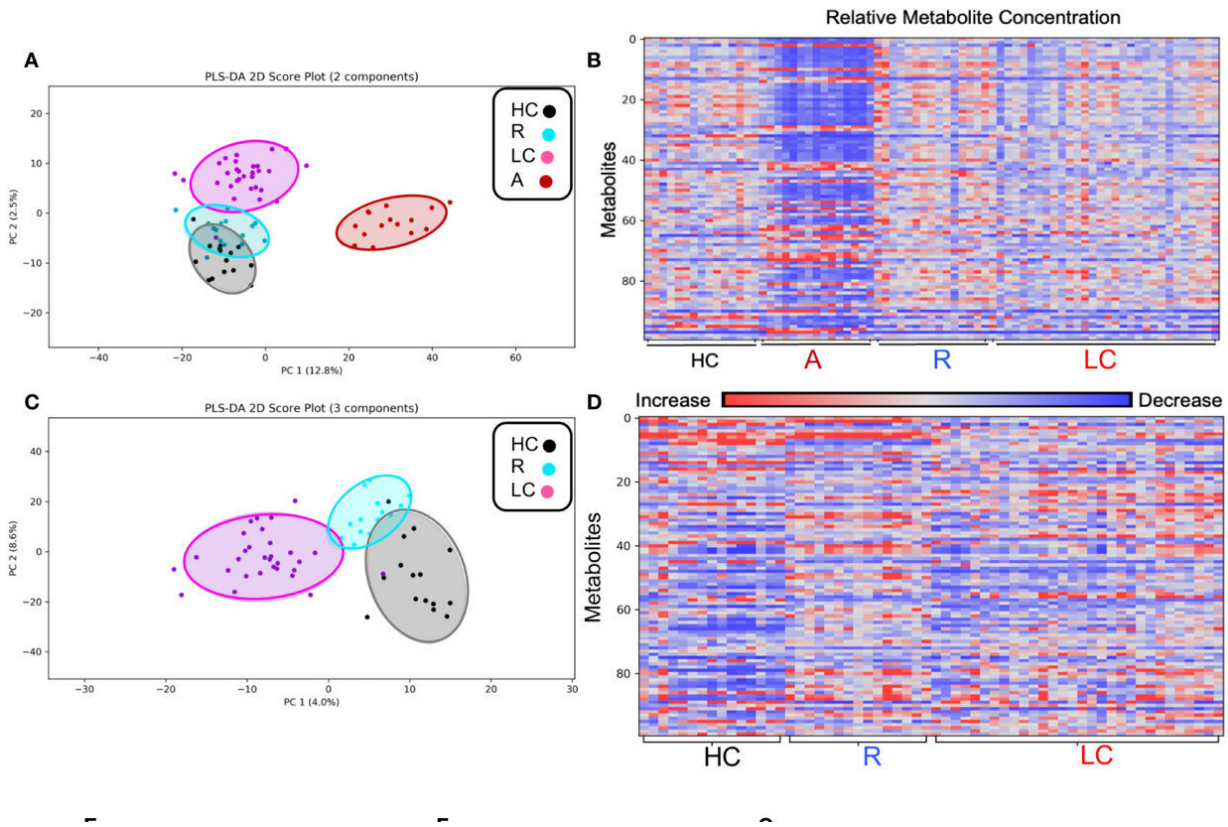

Altered metabolomic profile in SARS-CoV-2 infected individuals. Credit: *Frontiers in Immunology* (2024). DOI: 10.3389/fimmu.2024.1341843

A University of Alberta research team brings together immunologists,

virologists, rheumatologists and metabolomics experts in an effort to discover exactly what is ailing the sickest long COVID patients and find treatments for them.

In research recently published in *Frontiers in Immunology*, the team reports that a disproportionate number of people affected—nearly 70%—are female and face debilitating symptoms that are identical to chronic fatigue syndrome, now referred to as myalgic encephalomyelitis/chronic fatigue syndrome or ME/CFS. Blood samples show telltale amino acid deficiencies, suggesting readily available supplements have potential as therapy.

Statistics Canada reports that 1 in 9 Canadians had post-COVID-19 condition or "long COVID" by June 2023, meaning they experienced continuing symptoms three or more months after infection. As many as 60% of patients with symptoms at 12 months experience the most severe, chronic fatigue syndrome symptoms.

"We do not actually believe that long COVID is a separate new disease," explains rheumatologist and clinical immunologist Jan Willem Cohen Tervaert, professor of medicine, who is an expert in fatigue associated with rheumatic illnesses.

"Some symptoms—such as the loss of taste and chest pain—are very specific for COVID, but we see a common pathway with ME/CFS, which leads to the same fatigue, brain fog, post-exertional malaise, widespread pain and non-refreshing sleep," he says.

More women than men are likely affected because females have more robust immune systems, explains immunologist Shokrollah Elahi, professor in the School of Dentistry and principal investigator on the study.

"This robust immune response protects women at the acute phase of disease, so we see that mortality is higher in men, but later on it can result in collateral damage in women from a hyper-immune response," says Elahi.

Persistent abnormalities

For the study, the researchers carried out clinical exams and analyzed blood samples from 75 people. Fifteen of them had never been exposed to SARS-CoV-2, the virus that causes COVID-19, and were used as a healthy control group.

Thirty patients had persistent severe long COVID symptoms 12 months after their acute infection that met the criteria for a ME/CFS diagnosis. Fifteen others were hospitalized at the time of their acute infection but then recovered fully, and 15 had the infection but never developed acute or long-lasting symptoms. All 60 COVID cases were confirmed as the Wuhan viral strain in 2020 using molecular testing at the University of Alberta Hospital.

Analysis at Canada's Metabolomics Innovation Center, based at the U of A, showed that all of the people who had acute COVID exhibited some changes, but the 30 long COVID patients exhibited several persistent metabolomic abnormalities 12 months after their acute illness.

The first change the researchers noted was abnormally low levels of adenosine triphosphate (ATP), which is the cellular source of energy, likely due to mitochondrial dysfunction caused by the disease.

"Mitochondria are like the powerhouses of the cell, generating ATP, which is like a rechargeable battery that provides power to cells," Elahi explains. "When those two are not working properly, it may explain why these patients are always tired—they simply don't have enough energy to

function and carry out their routine activities."

Next, the team noted signs of chronic systemic inflammation, including finding markers of compromised gut integrity resulting in gut products leaking into the blood—a problem often observed in patients with HIV.

Finally, the researchers noted significantly lower-than-normal levels of the amino acids sarcosine, glutamine and serine in the plasma of the long COVID patients. All three are associated with normal brain function. Sarcosine is used as a supplement to treat depression and schizophrenia, low glutamine can cause the gut to leak, and low serine is associated with seizures and learning difficulties.

Strikingly, the team found that long COVID patients with lower plasma levels of these amino acids were more likely to report symptoms of clinical depression, anxiety and mental impairment.

An ongoing search for answers

Cohen Tervaert and Elahi hope to study the amino acid deficiencies further in animal models and would also like to do further research to determine whether sarcosine supplements, in particular, for patients with long COVID.

"The goal is to treat patients and help them get better," says Cohen Tervaert. "The sarcosine option is completely new, so that's why it's important."

Elahi is focused on a soon-to-be-published paper on RNA sequencing of an even larger group of long COVID patients.

"We are looking at the genes to identify the cause of all these changes in long COVID patients," he says.

Cohen Tervaert hopes the work will lead to more research involving patients with ME/CFS in general.

"ME/CFS has been labeled as a psychosomatic disease, and patients still have to fight for recognition by their doctors and their peers," he says. "For some, they can never leave their beds again. It really is a disease that needs more attention."

More information: Suguru Saito et al, Metabolomic and immune alterations in long COVID patients with chronic fatigue syndrome, *Frontiers in Immunology* (2024). DOI: 10.3389/fimmu.2024.1341843

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