PRESS RELEASE

COPER study: a national study explores the pathophysiological causes of long COVID

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While the long-term consequences of severe COVID-19 are well documented, the mechanisms behind persistent symptoms after a mild form of the disease remain largely unknown. Researchers from the Institut Pierre Louis d'Epidémiologie et de Santé Publique (IPLESP), a Sorbonne University and Inserm research laboratory, in a study coordinated by ~~the~~ ANRS Emerging infectious diseases (ANRS MIE), presents the results of the COPER study. This study offers new insight into the links between long-lasting COVID-19 effects (known as PASC - *Post-Acute Sequelae of* COVID-19- or long COVID) and immuno-inflammatory abnormalities in non-hospitalized patients. The study reveals complex relationships between variations in certain biomarkers, types of persistent symptoms and time since infection. The project has been designated a National Research Priority by the Strategic Orientation Committee on Clinical Trials and Other Research on COVID-19 (CAPNET), and funded by the French Ministry of Health and Prevention and the Ministry of Higher Education, Research and Innovation. This work is published in the journal *eBioMedicine* , on June 1st2025.

The persistent neurological, cardiovascular and respiratory sequelae of COVID-19, known as PASC (*Post-Acute Sequelae of COVID-19*), are not limited to severe forms. At the end of 2022, a critical review of the scientific literature highlighted the many hypotheses being explored to explain long COVID: viral persistence, immune dysregulation, chronic inflammation, endothelial dysfunction, coagulation disorders, autoimmunity and mitochondrial damage. While some studies support these hypotheses with biomarkers (IL-6, IFNγ, TNF-α, etc.), numerous methodological limitations have been identified : small numbers, absence of control groups, lack of statistical adjustment, and above all, frequent exclusion of non-hospitalized patients - even though they constitute the majority of cases of PASC.

A large-scale study on long COVID

The COPER study, launched in 2022, hypothesizes that the variability in clinical symptoms can be attributed to several underlying mechanisms. To investigate this hypothesis, a sufficiently large cohort has been assembled to examine symptoms, biomarkers and their evolution over time.

Between June and November 2022, 1,000 participants from general population cohorts (CONSTANCE, E3N-generation, Nutrinet-Santé) were included. A total of 801 participants were included in this initial work, divided into two groups: a group of people fully recovered from SARS-COV-2 infection (n = 490), and a group still suffering from persistent symptoms (n = 311), such as fatigue, shortness of breath, cough or sleep disturbance. No participants were hospitalized. The aim of the study was to better understand the biological mechanisms underlying the persistent symptoms observed after SARS-CoV-2 infection in non-hospitalized patients.

Biological differences in certain symptomatic patients

Biological analyses carried out during two home visits six months apart revealed significant associations between certain blood biomarkers and persistent symptoms, particularly those linked to viral activation, COVID-19 severity and vascular inflammation. However, these abnormalities did not appear to last over time, suggesting the transient nature of certain mechanisms.

"*One of the conclusions of the study is that analyzing inflammatory markers is probably insufficient to discriminate between people suffering from long COVID. Studies using a similar methodology and taking into account other biomarkers need to be carried out*" Olivier Robineau, University of Lille.

Conclusion

Beyond the logistical success of implementing such a study - including collaboration between different cohorts, the organization of home visits and the transport of samples from all over France - this first publication from this cohort highlights the clinical and biological heterogeneity of long COVID, as well as the influence of time since infection on the biomarkers analyzed.

It underlines the importance of "multi-omics" studies, i.e. an integrated approach combining several types of data (genomics, transcriptomics, proteomics, metabolomics, etc.) to obtain a global, multidimensional view of the processes potentially involved in post-infectious syndromes. This type of study requires substantial funding. A system of this type and the methodology used could be applied to the study of persistent symptoms occurring after other infections, in the context of epidemics and the emergence of new pathogens spreading through the general population.

"The first therapeutic trials were disappointing in terms of medical treatment, perhaps because of the heterogeneity of the patients included. Our study suggests that therapeutic research will have to take into account at least the symptoms and the time since infection to create the most homogeneous study groups possible. We are moving towards personalized or precision medicine". Olivier Robineau, University of Lille.

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