PRESS RELEASE

A scientific day for long Covid research

Paris, 17 October 2024

On 14 October 2024, ANRS Emerging Infectious Diseases, in partnership with *Santé publique France* and the French National Authority for Health (HAS), organised a scientific day dedicated to research on long Covid. A milestone for research, the day was marked by discussions and exchanges between researchers, clinicians, associations and the institutional world, to help define the main directions for future research.

Patient follow-up has shown that the wide range of post-Covid symptoms, grouped together under the name long Covid, probably includes **multiple symptoms that are still insufficiently understood.**

The complexity of the disease demonstrated by the wide variety of symptoms does not fall within the remit of any particular speciality or discipline. **Interdisciplinary dialogue and coordination between the various players, including patients and associations, must be strengthened and improved.** Resolving the Covid-19 crisis required an exceptional international effort. A similar commitment is essential for long Covid**.**

A day for long Covid research

For ANRS Emerging Infectious Diseases (ANRS MIE), research must involve people living with the disease from the outset, from conception to analysis and completion of the study. The event was organised **in partnership with *Santé publique France* and the *Haute Autorité de santé*,** and with the help of **patient associations** (*ApresJ20: Association Covid long France, Association Covid long enfants, Association Winslow santé publique*), which took part in selection committees, the scientific advisory board and moderated plenary sessions.

The event covered several areas of research: epidemiology, pathophysiology and clinical trials. Researchers and clinicians presented their work on the underlying mechanisms of the disease, which will help better characterise the post-Covid syndrome(s), understand the clinical forms in order to improve diagnosis and patient care.

A summary of the day's presentations is appended to the end of this press release.

Prioritise future research using a coordinated, multidisciplinary approach that includes patients

The aim of the event was to take **research to the next level.** The pathophysiological and epidemiological hypotheses presented have prompted us to rethink our priorities and should be used to define new main research objectives.

A number of key points emerged from this first meeting:

- More attention needs to be paid to paediatric patients. Long-term monitoring is also essential.
- Epidemiology has made it possible to quantify the burden of the disease and identify multiple risk factors, linked to the infection (severity, number, wave and variant), the demographic context (sex, age), the social context (working conditions, representations), the pathological context (burden of physical and psychological co-morbidities) and behaviour (vaccination).
- Preparedness for future epidemics and pandemics is a key driver of research into emerging infectious diseases. Epidemiological knowledge, which several French teams have contributed to develop, should help to define, steer and evaluate public health policies aimed at reducing the disease burden on the population and preparing the healthcare system for future infections, as well as providing avenues for clinical and basic research in pathology.
- SARS-CoV-2 persistence and neuroinvasion of the central nervous system (CNS) have been demonstrated, but the impact on the CNS, the mechanisms involved and the links with neuropsychiatric symptoms and cognitive deficits need to be better understood.
- Pathophysiological studies should be continued and extended to other post-infectious syndromes (post-influenza, dengue fever, Lyme borreliosis, etc.), on the assumption that they share at least some of the same pathophysiological mechanisms.
- New therapeutic trials need to be set up. They must be multi-centre, and eligibility should be based on careful consideration of relevant biological and imaging markers and standardised clinical indicators.
- Patients must be involved in the design of clinical trials and the establishment of cohorts.

Finally, addressing these issues requires the continuation and progressive development of a research programme, as well as the coordination of multidisciplinary teams including epidemiologists, basic researchers and clinicians (virologists, infectious disease specialists, neurologists, lung specialists, cardiologists, etc.). These teams need to be committed over the long term, with funding and infrastructures. They need to be organised at national level and seek to integrate better into the international research effort.

Among those taking part in this first scientific day were:

- Professor Lionel Collet, Chairman of the French National Authority for Health (HAS)
- Prof. Didier Samuel, Chairman and CEO of Inserm
- Dr Caroline Semaille, Director of *Santé publique France*
- Prof. Yazdan Yazdanpanah, Director of the ANRS Emerging Infectious Diseases
- Julie Lagrave, Head of the Research and Access to Innovation Unit, General Directorate for Healthcare Provision (DGOS), Ministry of Health
- Pauline Oustric: President of *ApresJ20: Association Covid long France*
- Ms Isabelle Leibl: *Association Covid long enfants*
- Solenn Tanguy: President of *Association Winslow santé publique*

Press contacts:
ANRS Emerging Infectious Diseases: presse@anrs.fr
High Authority for Health (HAS): contact.presse@has-sante.fr

About ANRS MIE: ANRS Emerging Infectious Diseases is an autonomous agency of Inserm (the French National Institute for Health and Medical Research). Its mission is to facilitate, evaluate, coordinate and fund research into HIV/AIDS, viral hepatitis, sexually transmitted infections, tuberculosis and emerging and re-emerging infectious diseases.

For more information: https://anrs.fr/en/

About *Santé publique France*: *Santé publique France* is France's centre of reference and expertise in public health. Founded on the continuum between knowledge and action, our mission is to protect and improve public health. Our work covers all the major public health issues over the long term: from protection against threats (in particular infectious risks, environmental risks, health determinants, etc.) to improving health (prevention, health promotion targeting the reduction of disease burden and social and territorial inequalities, etc.). *Santé publique France* is a public body under the supervision of the Ministry of Health.

For more information: https://www.santepubliquefrance.fr/

About the French National Authority for Healthcare (HAS): As an independent public scientific authority, HAS aims to develop quality in healthcare, social and medico-social fields. It works alongside public authorities to inform their decision-making, with professionals to optimise their practices, and for users, helping them to make their own choices. HAS has three main missions. It is responsible for evaluating medicinal products, medical devices and other health interventions in view to their reimbursement. HAS also develops recommendations on best practices, vaccination and public health. Finally, HAS is responsible for measuring and improving quality care and patient safety in health care facilities and office-based practice, as well as supporting quality in social care servics and facilities. HAS carries out its activity in accordance with three core values: scientific rigour, independence and transparency.

For more information: https://www.has-sante.fr/jcms/pprd_2986129/en/home

Please note that DeepL tool was used for translation

APPENDIX

SESSION 1: Epidemiology and population studies

Defining and measuring the burden of long Covid in the general population: the contribution of cross-sectional surveys

Tatjana Makovski (Santé publique France)

The multiplicity of methodological approaches, and in particular the diversity of definitions, makes it difficult to measure the prevalence of long Covid in the general population and to compare studies carried out in different countries. In France, Santé publique France has carried out two studies in the general population, one using a quota sampling method and conducted via the internet in March-April 2022, and one using a random sample and a detailed questionnaire by telephone or internet in November-December 2022.

The presentation focuses on the influence of the definitions of long Covid used on the prevalence measured. According to WHO criteria, 4% of the general population was classified as having a post-Covid condition in each of the two surveys. Among people reporting confirmed or probable infection with SARS-Cov-2 for more than three months (13% in March-April, 48% in November-December), the proportion meeting the WHO definition was 30% and 8% respectively.

This may be explained by the combined effect of the increase in the population affected between the two surveys and the reduction in the risk of post-Covid-19 disease in the context of the Omicron wave infections. In the second survey, 30.9% of people meeting the definition of long-standing Covid had been infected for more than 12 months, and 22.4% for more than 18 months.

The concordance of the prevalence of post-Covid syndrome was assessed using a kappa coefficient based on data from the November-December 2022 study between the standard WHO definition and those used elsewhere. There was little agreement between the four definitions used:

- WHO reinforced: moderate (2.4%) or strong/very strong (1.2%) impact on activities of daily living
- NICE (UK): at least one symptom (8.6%), or at least two symptoms (4.0%), lasting ≥ 12 weeks, and not explained by another diagnosis
- CDC/NCHS (United States): at least one symptom lasting ≥ 12 weeks and with an impact on daily functioning (7.6%)
- UK OS: at least one symptom, lasting ≥ 4 weeks and not explained by another diagnosis (13.4%)
- Yes answer to the question "Do you consider that you have had a long form of Covid-19": 7.1%.

In the American studies conducted regularly until spring 2024, the prevalence shows only a slight decrease over time. In view of these trends, monitoring of long-onset COVID, and in particular post-COVID-19 disease, merits discussion in France. In conclusion, the prevalence of long-COVID in the general population, the persistence of symptoms over time, the fact that long-COVID affects people of working age, and the burden on the healthcare system all suggest that epidemiological measures should be continued.

Period of infection and long Covid in the general population: contributions of the EpiCov cohort

Anne Pastorello (Université Paris Saclay, Inserm, Paris)

A number of studies have highlighted a reduction in the risk of post-Covid symptoms from 2021 onwards, linked to the spread of vaccination against SARS-Cov-2 in the general population[1] and the arrival of new variants of the virus (Omicron in particular)[2] . On the other hand, few studies have looked at changes that may have occurred from the start of the pandemic. Using data from EpiCov, a socio-epidemiological cohort representative of the general population living in France, we compared the risk of post-Covid symptoms at 6 months or more according to the period of the first acute covid: first (March-May 2020) or second epidemic wave (September-November 2020). We found a higher risk of post-Covid symptoms in the first (14.6%; 95% CI: 13.9%-15.3%) than in the second epidemic wave (7.0%; 95% CI: 6.3%-7.7%), including after adjustment for social, health and severity-related characteristics of the acute Covid (adjusted relative risk: 1.36; 95% CI: 1.20-1.55). As the first two epidemic waves occurred before the dissemination of vaccines against SARS-Cov-2 and before the appearance of new variants of the virus in France[3] , the difference observed cannot be explained by either of these two phenomena. On the other hand, the context of acute infection could play a role in the persistence of symptoms over the long term.

References :

1. Ceban F, Kulzhabayeva D, Rodrigues NB, et al. COVID-19 vaccination for the prevention and treatment of long COVID: A systematic review and meta-analysis. *Brain Behav Immun*. 2023;111:211-229. doi:10.1016/j.bbi.2023.03.022
2. Fernández-de-Las-Peñas C, Notarte KI, Peligro PJ, et al. Long-COVID Symptoms in Individuals Infected with Different SARS-CoV-2 Variants of Concern: A Systematic Review of the Literature. *Viruses*. 2022;14(12):2629. doi:10.3390/v14122629
3. Coronavirus: key figures and trends in COVID-19 in France and worldwide. https://www.santepubliquefrance.fr/dossiers/coronavirus-covid-19/coronavirus-chiffrescles-et-evolution-de-la-covid-19-en-france-et-dans-le-monde

Risk factors for long Covid in the general population: contributions of the Constances cohort

Cédric Lemogne (Université Paris Cité, and Université Sorbonne Paris Nord, Inserm, INRAE, Centre de Recherche en Epidémiologie et StatistiqueS (CRESS), Paris, France, Service de Psychiatrie de l'adulte, AP-HP, Hôpital Hôtel-Dieu, Paris, France)

The persistence of physical symptoms despite the 'biological cure' of an acute illness or the 'biological remission' of a chronic disease is a frequent observation in medicine. Unsurprisingly, the same phenomenon is observed in COVID-19. In addition to mechanisms specific to each disease, this suggests the existence of transnosographic mechanisms for the persistence of symptoms, whatever their origin. Some of these mechanisms are modifiable and therefore constitute potential targets for treatment and prevention. This is particularly true of anxiety and depressive symptoms, which are associated with an increased risk of persistent symptoms after an acute infection. Thanks to data from the CONSTANCES cohort and support from ANRS MIE, we were able to show that the presence of anxious or depressive symptoms before or at the start of the pandemic was associated with an increased incidence of persistent symptoms, independently of SARS-CoV-2 infection. In addition, depressive symptoms during the first wave explained 40% of the increased risk of such symptoms for women in the event of infection. In the long Covid, the correlation between the symptoms suffered by patients and the signs observed by doctors (including the results of biological investigations) is often weak or even non-existent. In reality, this correlation is always relative in medicine, suggesting a

continuum between 'organic' symptoms (strong correlation) and 'functional' symptoms (weak correlation).

Consistent with this hypothesis, the presence of functional dyspnoea at inclusion in CONSTANCES was associated with an increased incidence of all types of persistent symptoms, independent of SARS-CoV-2 infection. These results suggest that research into long Covid should not be limited to mechanisms specific to SARS-CoV-2.

References :

1. Lemogne et al. Why the hypothesis of psychological mechanisms in long COVID is worth considering. *J Psychosom Res*. **2023**;165:111135. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9825049/
2. Matta J, et al. Depressive symptoms and sex differences in the risk of post-COVID-19 persistent symptoms: a prospective population-based cohort study. *Nat. Mental Health*. **2024**;2:1053-1061. https://doi.org/10.1038/s44220-024-00290-6
3. Lemogne C, et al. National committee statement as a missed opportunity to acknowledge the relevance of a biopsychosocial approach in understanding long COVID. *J Psychosom Res*. **2024**;186:111596. https://www.sciencedirect.com/science/article/abs/pii/S0022399924000084?via%3Dihub

Long Covid integrative risk model

Cyrille Delpierre (Inserm, Toulouse)

Various factors, linked to Covid-19 infection, but also to socio-demographic characteristics, initial state of health (mental and physical), health behaviours and, more generally, living conditions, have been found to be associated with long COVID. However, most of these factors are not independent and have rarely been analysed in the same model, which limits our understanding of the aetiology of long-term IRVC. Based on a review of the literature, we have proposed a conceptual model that integrates these different factors in a logical way, a model that we have evaluated in a study conducted after the Omicron waves in autumn 2022 on a representative sample of 1,813 adults. The results show that the prevalence of long Covid varies according to the definitions used. However, whatever the definition, the results support our conceptual model and the influence of the different categories of risk factors tested.

The wide range of factors confirmed or discovered in this work suggests that long Covid should be considered not only as a direct complication of SARS-CoV-2 infection, but also as the result of a wider network of contextual, medical, psychological and social factors. These factors should be better taken into account when developing prevention and management strategies. The article corresponding to this work is in the process of being published, so the results presented are confidential at this stage.

References :

1. Coste J, Delpierre C, Richard JB, Alleaume C, Gallay A, Tebeka S, Lemogne C, Robineau O, Steichen O, Makovski TT. Prevalence of long COVID in the general adult population according to different definitions and sociodemographic and infection characteristics. A nationwide random sampling survey in France in autumn 2022. Clin Microbiol Infect. 2024 Jul;30(7):924-929.
2. Luo D, Mei B, Wang P, Li X, Chen X, Wei G, Kuang F, et al. Prevalence and risk factors for persistent symptoms after COVID-19: a systematic review and meta-analysis. Clin Microbiol Infect 2023:S1198-743X(23)00526-8.
3. Tsampasian V, Elghazaly H, Chattopadhyay R, Debski M, Naing TKP, Garg P, et al. Risk Factors Associated With Post-COVID-19 Condition: A Systematic Review and Meta-analysis. JAMA Intern Med 2023;183:566-80.

SESSION 2.1 Pathophysiology (part 1)

Exploring NK cell memory and tissue residence in the context of long Covid

Nicolas Huot (HIPER Unit, Institut Pasteur, Paris)

In the context of SARS-CoV-2 infection, NK (*Natural Killer*) cells play a key role in the innate immune response by eliminating infected cells. The THEMIS protein, traditionally associated with T cell maturation, may also play an important role in regulating NK cell activity during SARS-CoV-2 infection.

Characterisation of NK cells expressing THEMIS is essential to understand how this protein influences the ability of NK cells to respond to the virus. THEMIS could modulate signalling pathways involved in the antiviral response, in particular via the cytokines IL-2 and IL-15, which are crucial for the activation and survival of NK cells. Dysfunction of THEMIS in this context could affect the effectiveness of the immune response against SARS-CoV-2, thereby contributing to more severe forms of the disease or prolonged sequelae, such as post-COVID syndrome (long COVID).

This study will provide a better understanding of how THEMIS influences the homeostasis and function of NK cells during infection. It could open up new therapeutic prospects for improving the immune response in patients with Covid-19.

References :

1. Hasan MZ, Claus M, Krüger N, et al. *SARS-CoV-2 infection induces adaptive NK cell responses by spike protein-mediated induction of HLA-E expression*. Emerg Microbes Infect. 2024 Dec;13(1):2361019. doi: 10.1080/22221751.2024.2361019. Epub 2024 Jun 27. PMID: 38804979; PMCID: PMC11212573.
2. Huot N, Planchais C, Rosenbaum P, et al. *SARS-CoV-2 viral persistence in lung alveolar macrophages is controlled by IFN-γ and NK cells*. Nat Immunol. 2023 Dec;24(12):2068-2079. doi: 10.1038/s41590-023-01661-4. Epub 2023 Nov 2. PMID: 37919524; PMCID: PMC10681903.
3. Witkowski M, Tizian C, Ferreira-Gomes M, et al. *Untimely TGFβ responses in COVID-19 limit antiviral functions of NK cells*. Nature. 2021 Dec;600(7888):295-301. doi: 10.1038/s41586-021-04142-6. Epub 2021 Oct 25. PMID: 34695836.

Neuroinvasion and the impact of long-term infection on the brain

Guilherme Dias de Melo (Lyssavirus Epidemiology and Neuropathology Unit, Global Health Department, Institut Pasteur, Paris)

It is increasingly clear that SARS-CoV-2 infection does not only affect the airways, but also the central nervous system (CNS), sometimes leading to long-lasting signs, including neuropsychiatric manifestations and cognitive deficits. Our working hypothesis is that SARS-CoV-2 and the related inflammatory response can trigger a central mechanism in the CNS leading to symptoms persistence. We previously demonstrated that different variants of SARS-CoV-2 could invade the brain via the olfactory bulbs. We are now focusing on the brainstem and the occurrence of neuropsychiatric and cognitive symptoms in the post-acute phases. To that, we developed and characterized a long Covid model in golden hamsters, and as observed in human patients, SARS-CoV-2 infection induced prolonged, sometimes relapsing, behavioral changes including anxiety, depression and memory impairment. In the acute phase, the brainstem suffers from viral replication and an unbalanced

innate immune response. Remarkably, some brainstems were still infected in the post-acute phase. Overall, this work will improve our understanding of the spatiotemporal dynamics of SARS-CoV-2 infection, from entry into the brain to long-term CNS alterations. Unveiling these fundamental mechanisms should be of broad interest to the scientific community, as these results may be applicable to other, less understood, neuroinvasive pathogens, whose infectious process may result in neuropsychiatric symptoms and cognitive impairment.

References

1. Coleon A, et al. Long-term neuropsychiatric and cognitive consequences of COVID-19 are associated with altered brainstem transcriptome and persisting infection in the hamster model of long COVID. submitted. 2024.
2. de Melo, GD et al. Neuroinvasion and anosmia are independent phenomena upon infection with SARS-CoV-2 and its variants. Nature Communications 14, 4485 (2023)
3. de Melo GD, Lazarini F, Levallois S, Hautefort C et al. COVID-19-related anosmia is associated with viral persistence and inflammation in human olfactory epithelium and brain infection in hamsters. Science Translational Medicine 13, eabf8396 (2021)

Immune and metabolic dysregulation in long COVID patients: from diagnosis to therapy

Mireille Laforge (Inserm, Université Paris Cité, Paris)

Evidence of a persistent antiviral immune response in long Covid

Darragh Duffy (Institut Pasteur, Paris)

Long Covid is a frequent and complex condition that manifests itself through a variety of symptoms following acute infection with SARS-CoV-2. The pathophysiology often resembles an overactive immune response. The key question is therefore what drives these deregulated immune responses.

With regard to the hypothesis that residual virus causes ongoing low-level immune activation with a variety of symptoms, I will summarise the studies that support (or do not support) this hypothesis, including the following: (i) Detection of SARS-CoV-2 after resolution of acute infection; (ii) Detection of SARS-CoV-2 preferentially in patients with long-term conditions (iii) Evidence of dysregulation of innate antiviral immunity in long Covid patients (iv) Evidence of dysregulation of adaptive immunity or breakdown of tolerance in long Covid patients. I will conclude by looking at how this knowledge is being used to develop new treatment strategies.

References :

1. Ghafari M, et al. Prevalence of persistent SARS-CoV-2 in a large community surveillance study. Nature. 2024 Feb;626(8001):1094-1101. doi: 10.1038/s41586-024-07029-4.
2. Menezes SM, et al. Blood transcriptomic analyses reveal persistent SARS-CoV-2 RNA and candidate biomarkers in post-COVID-19 condition. Lancet Microbe. 2024 Aug;5(8):100849. doi: 10.1016/S2666-5247(24)00055-7.
3. Santos Guedes de Sa K, et al. A causal link between autoantibodies and neurological symptoms in long COVID. medRxiv [Preprint]. 2024 Jun 19:2024.06.18.24309100. doi: 10.1101/2024.06.18.24309100.
4. August Jernbom Falk. Prevalent and persistent new-onset autoantibodies in mild to severe COVID-19. medRxiv 2024.02.15.24302857; doi: https://doi.org/10.1101/2024.02.15.24302857

SESSION 2.2 Pathophysiology (Part 2)

Role of the initial episode - immunodeficiency and long Covid

Sónia André (Inserm, University of Paris, Paris)

Following the SARS-CoV-2 pandemic in 2020, which resulted in the infection of more than 700 million people, the emergence of post-infectious symptoms has led to the notion of the long Covid. Our hypothesis is that the onset of an early immune deficiency contributes to the development of this pathology, which favours viral dissemination and persistent immunological alterations.

Our work has shown that in the early phase of infection, lymphopenia, observed in 60% of infected individuals, is associated with T-cell apoptosis. This programmed cell death involves specific receptors, mitochondrial damage and DNA damage, caused in particular by the production of reactive oxygen species (ROS) by monocytes. Our results show that the onset of this apoptosis is negatively correlated with the establishment of the humoral response directed against SARS-CoV-2 antigens. This not only leads to a delay in the establishment of this humoral response but also affects the quality of the antibodies produced. For example, antibodies directed against the spike (S) protein are less effective in people with higher apoptosis. This could therefore encourage viral dissemination and chronic replication of SARS-CoV-2.

Our data suggest viral persistence in people with long-standing Covid, leading to alterations in the innate and adaptive immune response. A retrospective study in the early phase of infection showed that these patients had higher levels of inflammation and apoptosis. Our current work therefore aims to define more specifically the immunological mechanisms and the consequences of this apoptosis on the outcome of infected individuals in relation to their clinical profiles.

References

1. André S et al, 2022, Cell Death Differ 29:1486-1499
2. André S et al, 2022, Cell Death Dis 13:741
3. Cezar R, et al, 2024, Front Immunol 14:1335352

Seeing through fog: a neuroendocrine explanation of post-Covid cognitive disorders

Vincent Prévot (Inserm, Lille)

In this talk, we will examine two main hypotheses to explain some of the neurological alterations observed in people suffering from long Covid. The first hypothesis concerns damage to the endothelial cells of the blood-brain barrier[1]. These cells, infected by SARS-CoV-2, may undergo death by necroptosis, leading to the rupture of this protective barrier in the brain. This breach could allow various pathogenic agents (including the virus itself) or inflammatory molecules to enter the brain tissue, thereby contributing to the neurological symptoms of Long Covid. The second hypothesis involves gonadotropin-releasing hormone (GnRH), known for its role in cognitive functions.[2]. Disruption of the production or action of GnRH could be a key factor in the development of the neurological and cognitive deficits observed in patients with Long Covid.[3]. This is all the more interesting given that loss of GnRH is also associated with pathological cerebral ageing, suggesting potentially similar mechanisms.[4].

References

1. Wenzel, J. *et al.* The SARS-CoV-2 main protease M(pro) causes microvascular brain pathology by cleaving NEMO in brain endothelial cells. Nat Neurosci 24, 1522-1533, doi:10.1038/s41593-021-00926-1 (2021).
2. Manfredi-Lozano, M. et al. GnRH replacement rescues cognition in Down syndrome. Science 377, eabq4515, doi:10.1126/science.abq4515 (2022).
3. Sauve, F. et al. Long-COVID cognitive impairments and reproductive hormone deficits in men may stem from GnRH neuronal death. EBioMedicine 96, 104784, doi:10.1016/j.ebiom.2023.104784 (2023).
4. Rasika, S., Nogueiras, R., Schwaninger, M. & Prevot, V. Seeing through the fog: a neuroendocrine explanation for post-COVID cognitive deficits. Nat Rev Endocrinol, doi:10.1038/s41574-024-00955-3 (2024).

Impact of SARS-CoV-2 on synaptic homeostasis

Raphaël Gaudin (IRIM, CNRS, University of Montpellier, Montpellier)

In addition to the respiratory symptoms observed during the acute phase of SARS-CoV-2 infection, a variety of neurological disorders occur in many Covid-19 patients. These nervous system disorders also manifest themselves after patients have gone into remission, in particular the pronounced neurocognitive symptoms that have been associated with long-standing Covid. Cognitive functions are largely dependent on synaptic homeostasis. Using advanced brain organoid models, organotypic culture of ex vivo infected human brain explants and brain samples from patients who died of Covid-19, our team has shown that SARS-CoV-2 induces synaptic abnormalities. We demonstrated that the virus disrupted synaptic morphology, composition and function. We have also identified the molecular mechanisms associated with these disturbances. These results will provide a better understanding of the impact of SARS-CoV-2 on the central nervous system and enable us to envisage new therapeutic strategies to reduce the associated neurocognitive disorders.

References

1. Brain exposure to SARS-CoV-2 virions disrupts synaptic homeostasis. Partiot E, Hirschler A, Colomb C, Lutz W, Claeys T, Delalande F, Deffieu MS, Bare Y, Roels J, Gorda B, Bons J, Callon D, Andreoletti L, Labrousse M, Jacobs FMJ, Rigau V, Charlot B, Martens L, Carapito C, Ganesh G, Gaudin R#. Nature Microbiology. 2024 Apr. doi: 10.1038/s41564-024-01657-2.
2. Organotypic culture of human brain explants as a preclinical model for AI-driven antiviral studies. Partiot E, Gorda B, Lutz W, Lebrun S, Khalfi P, Mora S, Charlot B, Majzoub K, Desagher S, Ganesh G, Colomb C, Gaudin R#. EMBO Molecular Medicine. 2024 Mar. 10.1038/s44321-024-00039-9. Journal's cover April 2024.
3. Organotypic culture of post-mortem adult human brain explants exhibits synaptic plasticity. Iwasaki Y*, Bernou C*, Gorda B, Colomb S, Ganesh G#, Gaudin R#. Brain Stimulation. Aug 2024. doi: 10.1016/j.brs.2024.08.010.

SESSION 3: Children and long Covid

Long Covid in children: clinical presentation, investigations and management. Current state of knowledge

Aurélie Morand (Assistance Publique - Hôpitaux de Marseille (AP-HM), Marseille)

Post-infectious syndromes in paediatrics have been described since the Spanish flu epidemic at the beginning of the 20ème century (1). Long Covid in paediatrics has been described since spring 2020, in epidemic mode since the Covid pandemic. Depending on the study, the incidence may range from 5% to almost 25% of children, depending on the delay after acute infection (2). Symptoms are essentially functional (2), combining fatigue, tiredness, post-exertional malaise, chronic pain, etc., with a subnormal clinical examination. This symptomatology fluctuates with potential relapses, particularly in association with physical, cognitive or emotional exertion exceeding the tolerance threshold, and is improved by pacing. The pathophysiology is still poorly understood, and several mechanisms are probably involved (viral persistence, autoimmunity, dysbiosis, neuroinflammation and neurotransmission disorders, mast cell activation syndrome). Risk factors are suspected but as yet poorly established. The main aim of further investigations is to rule out differential diagnoses for which there is a validated treatment. Complementary examinations are generally normal, except for the possibility of cerebral hypometabolism in a typical *pattern* on 18 FDG PET brain scans (3), and frequent medullary hyperfixation on whole-body PET scans, although this is not systematic and is not recommended for making the diagnosis.

Paediatric long Covid leads to significant impairment of quality of life, with a drop in school performance, a risk of physical deconditioning, malnutrition and difficulties in maintaining social interactions (4). Management is essentially based on *pacing* (5), very gentle and progressive rehabilitation to avoid deconditioning, and psychological support with training in non-medicinal pain management and relaxation techniques. It is usually necessary to draw up an individualised accommodation plan with the school. In the event of significant repercussions, a request for long-term care and the drafting of a file with the Maison Départementale du Handicap are justified. No aetiological treatment has been proven to be effective, but symptomatic treatments are used on a case-by-case basis.

Preventing long sore throat in children is based on avoiding infection or re-infection. Vaccination is thought to be protective (it would therefore be important to discuss generalising paediatric vaccination by facilitating access to it) (2). In the event of infection, a period of convalescence followed by compliance with an appropriate pacing regimen are key (5). In conclusion: Long paediatric covid is a reality that needs to be managed appropriately. Studies are needed to assess its impact and develop appropriate preventive and curative therapies. Social care should be facilitated.

References :

1. Von Economo. Encephalitis lethargica. Wien Klin Wochenschr. 1917.
2. Camporesi et al. Characteristics and predictors of Long Covid in children: a 3-year prospective cohort study. eClinicalMedicine. 2024
3. Morand et al. Similar patterns of [18F]-FDG brain PET hypometabolism in paediatric and adult patients with long COVID: a paediatric case series. Eur J Nucl Med Mol Imaging. 2022
4. Stephenson et al. Long COVID (post-COVID-19 condition) in children: a modified Delphi process. Archives of Disease in Childhood 2022
5. Toepfner et al. Long COVID in pediatrics-epidemiology, diagnosis, and management. European Journal of Pediatrics. 2024

SESSION 4 Clinical trials

Overview of current **clinical trials**

Dominique Salmon (Institut Fournier, APHP, Paris)

The treatment of long Covid is currently symptomatic. Conclusive trials have demonstrated the efficacy of some of these symptomatic approaches (e.g. Ivabradine and POTS, antihistamines and secondary SAMA, respiratory rehabilitation and SHV, *pacing*) in long Covid. Recently, advances in pathophysiology have led to the development of so-called "causal" therapies. Among the hypotheses currently undergoing clinical trials are antiviral approaches directed against SARS CoV 2 or against the reactivation of other latent viruses (herpes virus, retrovirus), neuromodulation and immunomodulation approaches, approaches designed to promote tissue oxygenation (anticoagulants, hyperbaric oxygen) and rehabilitation approaches. In the absence of long Covid biomarkers yet available, the case selection and assessment criteria for these trials are purely clinical, often quite disparate and assessed at different times.

While it is very encouraging to see that many clinical trials are being set up, none of the so-called causal trials has yet demonstrated any marked efficacy in a randomised trial. It is therefore necessary to continue these trials, particularly those looking at combinations of antivirals and immunomodulators, to expand them in directions that have not yet been explored (mitochondrial dysfunction), and to initiate international discussions to harmonise the methodological criteria for clinical research on the long Covid.

References

1. Ghali A, Lacombe V, Ravaiau C, Delattre E, Ghali M, Urbanski G, Lavigne C. The relevance of pacing strategies in managing symptoms of post-COVID-19 syndrome. J Transl Med. 2023 Jun 8;21(1):375. doi: 10.1186/s12967-023-04229-w.
2. The Lancet Infectious Diseases. Where are the long COVID trials? Lancet Infect Dis. 2023 Aug;23(8):879. doi: 10.1016/S1473-3099(23)00440-1. PMID: 37507151.
3. Geng LN, et al. JAMA Intern Med. 2024 Sep 1;184(9):1024-1034. doi: 10.1001/jamainternmed.2024.2007. Erratum in: JAMA Intern Med. 2024 Sep 1;184(9):1137. doi: 10.1001/jamainternmed.2024.3735.
4. Trials testing an antiviral approach: ClinicalTrials.gov ID: NCT05576662; NCT05965726; NCT06161688; NCT05911906
5. Trials testing inhibition of reactivation of latent viruses (herpes viruses, retroviruses) ClinicalTrials.gov ID: NCT05911906 / NCT05497089; NCT06511063; NCT06316843/ tenofovir disoproxil/emtricitabine
6. Trials testing a neuromodulatory approach: ClinicalTrials.gov ID: NCT04604704 / NCT05430152 / NCT05690503/ NCT06234462/ NCT06055244 /NCT05618587/ NCT05874037/ NCT04904536/ NCT06586398/ NCT05389592
7. Trials testing an immumodulating approach: ClinicalTrials.gov ID: NCT05911009/ NCT05669261/NCT05926505/ NCT05946551
8. Trials testing hyperbaric oxygen therapy (HBOT): ClinicalTrials.gov ID NCT06118138/ NCT06267300 /NCT06452095/NCT06159309/ NCT04842448

Clinical trials - experience of multicentre RCTs on post-Covid

Mayssam Nehme (Geneva University Hospitals, Switzerland)

The GNC-501 clinical trial is a study conducted by Geneva University Hospitals. It is a phase 2 study in patients suffering from post-COVID-19 neuropsychiatric syndromes, which tested temelimab, a monoclonal antibody targeting the W-ENV protein, against a placebo. The scientific hypothesis was based on the finding that in vitro exposure to SARS-CoV-2 activates the expression of the pro-inflammatory envelope protein (ENV) of the human endogenous retrovirus (HERV) HERV-W (1-4). The aim of the study was to assess the efficacy and safety of temelimab in improving measures of fatigue and cognitive impairment associated with post-Covid.

The study involved more than 200 patients in Switzerland, Spain and Italy who had tested positive for HERV-W ENV (human endogenous retrovirus (HERV) research). The initial results of this study, released in June 2024 (5), show that treated patients did not show any clinically significant improvement over placebo on the primary endpoint measuring improvement in fatigue using the PROMIS SF7a test. The majority of secondary endpoints also showed no effect. The treatment was very well tolerated and safe, as in previous clinical trials in other indications. Preliminary analyses suggest that the shorter duration of disease at inclusion, as well as the evolution of underlying HERV-W ENV status, may have an impact on efficacy measures.

The results are currently being published, as it is important to publish results, even if they are negative, in order to advance research.

References

1. Grandi N, Tramontano E. Human Endogenous Retroviruses Are Ancient Acquired Elements Still Shaping Innate Immune Responses. Front Immunol 2018;9:2039.
2. Rodrigues LS, da Silva Nali LH, Leal COD, et al. HERV-K and HERV-W transcriptional activity in myalgic encephalomyelitis/chronic fatigue syndrome. Auto Immun Highlights 2019;10:12.
3. Charvet B, Brunel J, Pierquin J, et al. SARS-CoV-2 awakens ancient retroviral genes and the expression of proinflammatory HERV-W envelope protein in COVID-19 patients. iScience 2023;26:106604.
4. Balestrieri E, Minutolo A, Petrone V, et al. Evidence of the pathogenic HERV-W envelope expression in T lymphocytes in association with the respiratory outcome of COVID-19 patients. eBioMedicine 2021;66:103341.
5. https://geneuro.ch/wp-content/uploads/GeNeuro_GNC501-Results_28062024-2.pdf