Séminaire Data and Health – COVID long

Réunion d'animation scientifique autour du COVID-19

November 24, 2021

French research on Long COVID

5.1.2e Infectious and Tropical Diseases, Public Hospitals of Paris, University, Paris, France

Unresolved questions

- **Epidemiology of these persistent and resurgent symptoms**
  - The prevalence (about 15% at 6 months) maks heteroegeneity between severity of cases
  - Risk factors?
  - Duration, consequences and trajectories of patients

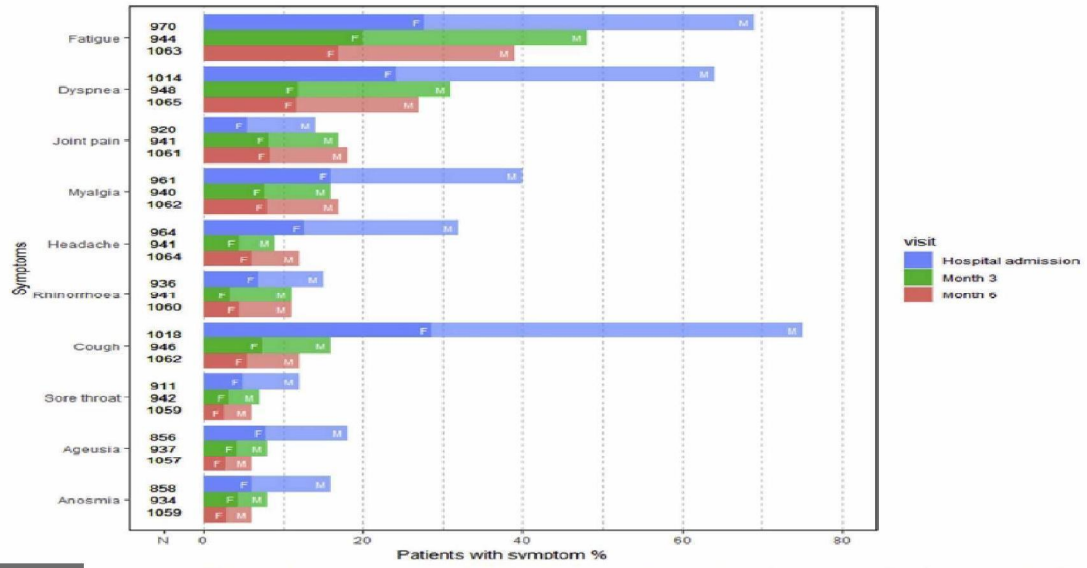
- **Pathophysiological mechanisms that cause symptoms?**
  - Viral persistence,
  - Immunity impairment, inflammatory responses, autoimmune factors
  - Other viral reactivation
  - Psychological or functional disorders
  - Genetic, hormonal factors

- **What therapeutic approaches should be proposed?**

- **What are the impacts on working life, social and family life?**

Some French contributions to the field

Persistent COVID-19 symptoms are highly prevalent 6 months after hospitalization : French COVID prospective cohort.

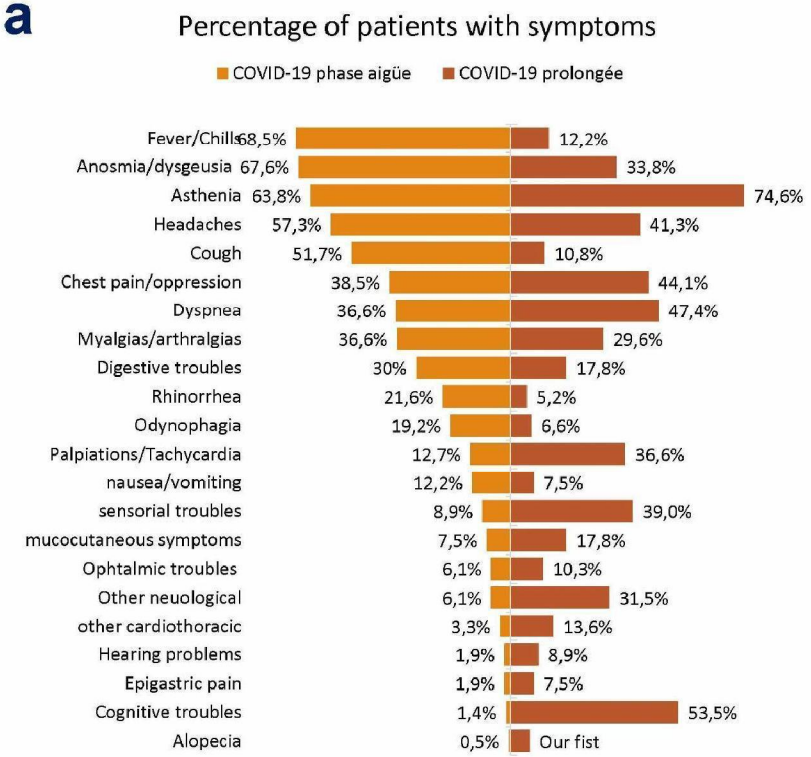


5.1.2e *Persistent COVID-19 symptoms are highly prevalent 6 months after hospitalization: results from a large prospective cohort. Clin Microbiol Infect. 2021 Jul;27(7):1041*

Persistent symptoms after a mild COVID : Long Covid Persicor cohort

Among 407 patients coming to the clinci for persistant resurgent symptoims, 68% had a documented infection

- **Female: 75%**
- **Median age : 45 [37-52]**
- **Atopy : 56.2%**
- **Personal or familial autoimmune history: 23.4%**
- Tobacco: 9.4%
- Health care worker : 25.6%
- Hospitalized (8%), O2 (2%)



5.1.2e *virological and imaging profile in patients with Persistent or resurgent forms of COVID-19: a cross-sectional study Infection, Janv 2021.*

Disabling multisystemic symptoms

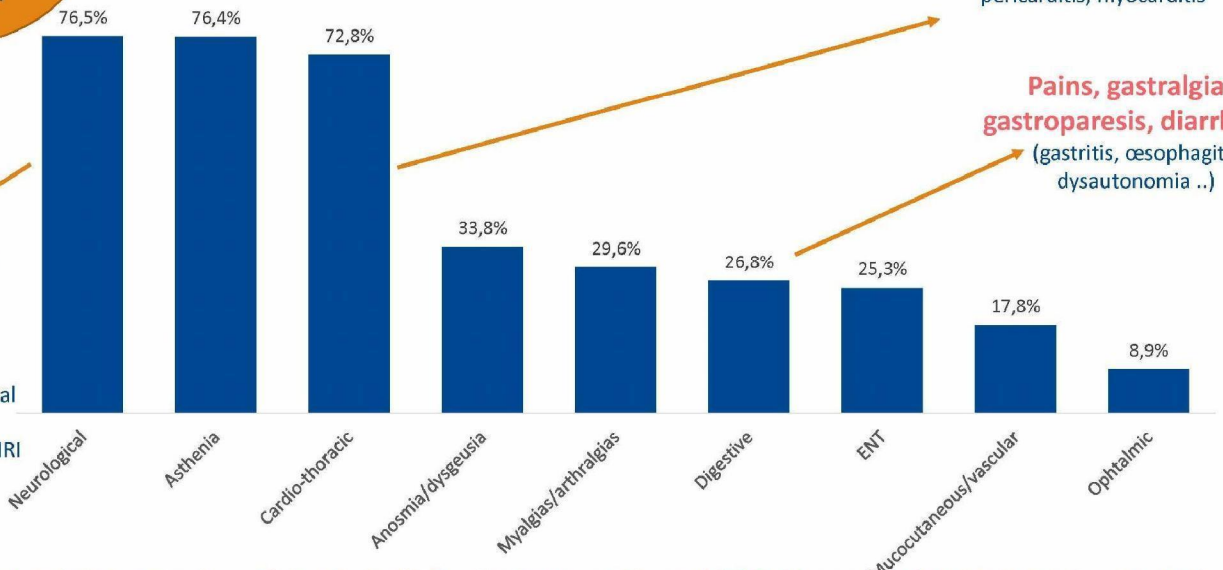
Fluctuating over several months

Triggering factors : physical/intellectual effort, stress, emotion, menstrual periods

Dyspnea, tachycardia chest pain, cough (hyperventilation syndrom, postural tachycardia (dyautonomia), less frequently pericarditis, myocarditis

Pains, gastralgias, gastroparesis, diarrhea,.. (gastritis, œsophagitis dysautonomia ..)

Cognitive impairment, sensory disturbances, sleep disturbances irritability, headache (disrupted neuropsychological assessment, TEP scanner hypometabolisms, normal MRI and EMG)

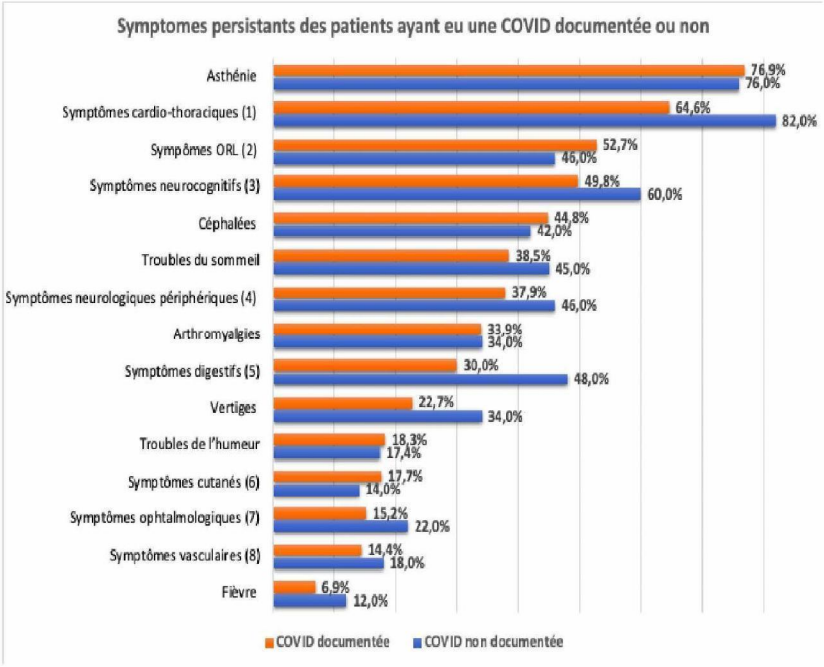


5.1.2e *Clinical, virological and imaging profile in patients with Persistent or resurgent forms of COVID-19: a cross-sectional study Infection, Janv 2021.*

Similar profile of persistent symptoms whatever the inital SARS COV 2 infection has been documented or not

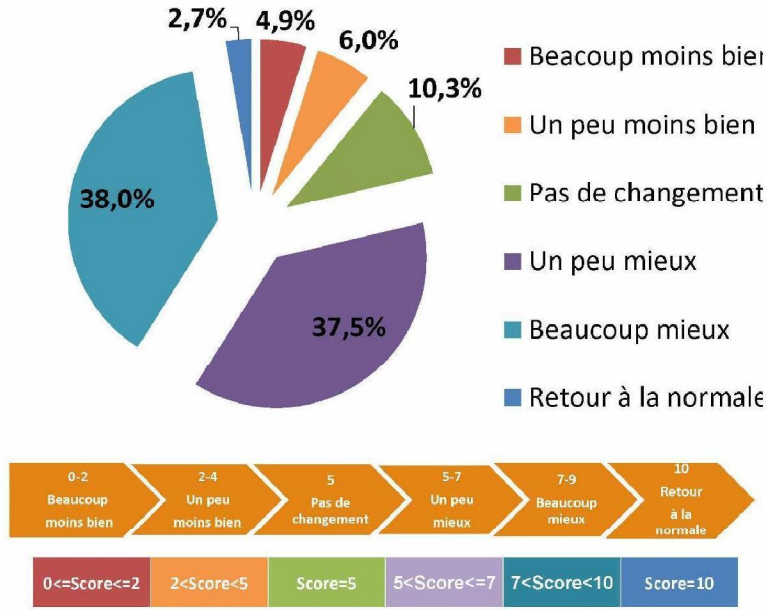
Among 357 long COVID cases seen between 05/2020 and 07/2021 at Hotel Dieu
- 277 documented infections (PCR ou séerology)
- 50 probable infections (WHO criteria)

Patients ayant eu une COVID-19 documentée	Patients ayant eu une COVID-19 possible	
Épisode initial symptomatique de la Covid-19 **confirmé** par au moins un critère parmi : -PCR SARS-CoV-2 + -Test antigénique SARS-CoV-2 + -Sérologie SARS-CoV-2 + -Anosmie/agueusie prolongée de survenue brutale -Scanner thoracique typique	**Fièvre** **Céphalée** **Fatigue** **Myalgie** **Dyspnée** **Toux** **Douleurs thoraciques** **Diarrhée** **Odynophagie**	Cumul d'au moins **3 critères**, de survenue brutale, dans un contexte épidémique



Une évolution lente vers l'amélioration

- Follow-up still short (1 year)
- Alternating phases of well-being and exacerbations triggered by physical or intellectual effort, emotions, menstruation, or meals;
- Based on a Score 1 to 10 "How do you feel about your pre-COVID state?" => global Improvement in 80%
- Among those who were employed, 93 (62.4%) did not return to work at 12 months. Of those who returned to work, 54 (98.2%) were part-time
- .



184 patients suivis à l'Hôtel Dieu à 12 mois (biais possibles)

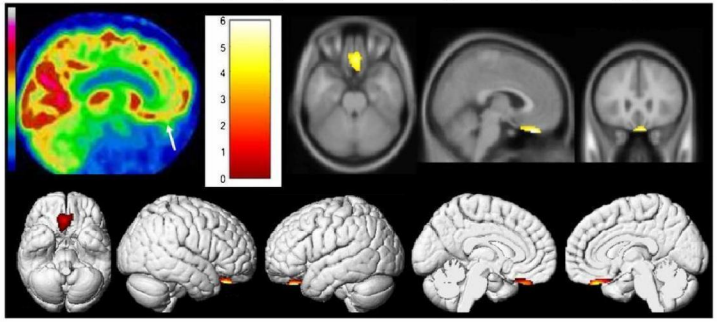
5.1.2e al. *One-year follow-up of Covid Long-haulers: A Longitudinal Study Among Non hospitalized Patients. ECCMID 2021*

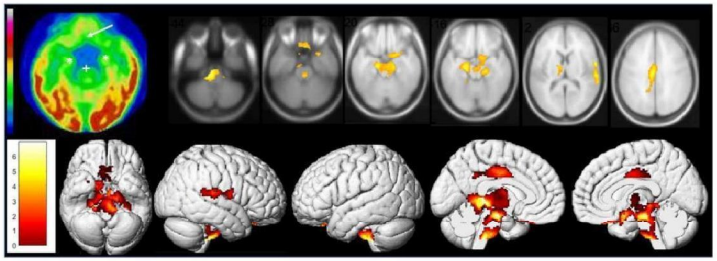
Viral persistence post infection in immunocompetent patients with long COVID and no nasopharyngeal swab tests

Authors,	Sex, age	Previous disease	Long COVID symptoms	SARS-CoV-2 Ab	Viral Shedding	Site
5.1.2e *Science Transl Med, 2021*	M24	None	Anosmia, parosmia, ageusia	NEG	110 d	Olfactory slit
	F43	Flammer syndrome	Anosmia, burning sensation, wriggling nose, left arm pain, intercostal pain	NEG	136 d	Olfactory slit
	F71	None	Hyposmia, ageusia, paresthesias, memory and concentration loss,	POS	158 d	Olfactory slit
	F56	None	Hyposmia, vertigo, queasiness, paresthesias, memory loss, chest pain, diarrhea , oesophagal pain	POS	196 d	Olfactory slit
	M 48	None	burning nose and head, queasiness, paresthesias, memory loss, vomiting, diarrhea, cough	NEG	156 d	Olfactory slit
5.1.2e *Infection 2021*	M 46	None	Asthenia, myalgia, neurological, ophthalmologic cardiothoracic signs, anosmia	POS	92 d	Pharynx
	F48	None	Asthenia, cardiothoracic signs	POS	107 d	Pharynx
	F37	None	Anosmia	POS	156 d	Pharynx
5.1.2e *Preprint*	M, 64	Atherosclerosis, HTA, diabetes	Low CD8 T and KC cells		196 d,	Nose sputum
5.1.2e *BMJ 2021*	5 pts	?	?		*9-180 d*	Digestive tract, bladder, lymph nodes

Cerebral hypometabolism in ^{18}F-FDG TEP scanner in longCovid :

bulbs/olfactive regions, amygdale/hippocampe, tronc cérébral, cervelet

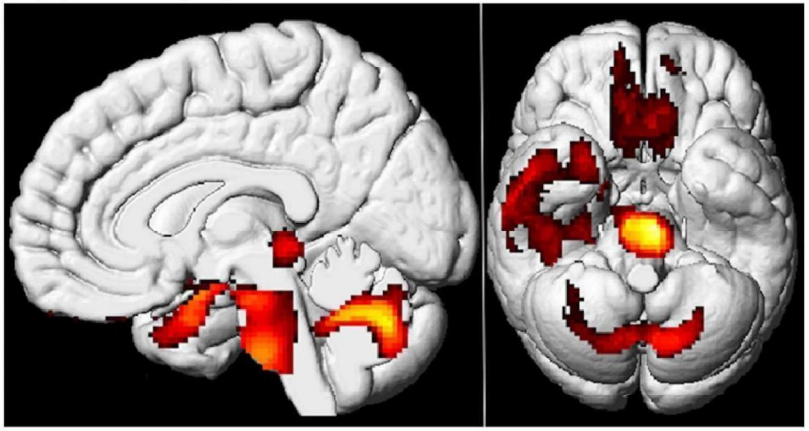




Exemple de 2 cas individuels

avec comparaison à une base de sujets sains; p < 0.001

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-020-04973-x



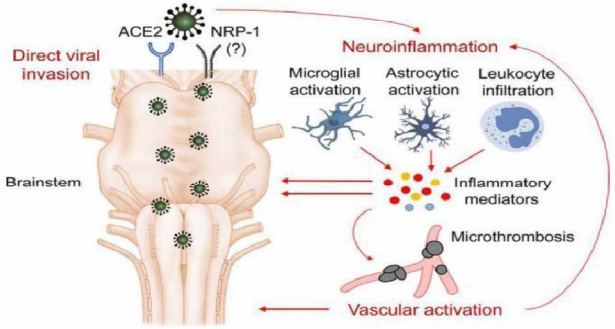
35 patients vs 44 sujets sains (p < 0.001)

- *L'hypométabolisme est corrélé à plus de symptômes (r = -0.581; p < 0.001), et en tendance à un Covid plus long (r = – 0.323; p = 0.058)*
- *100% de bonne classification entre patients et sujets sains*
- *Moins d'hypométabolisme chez patients traités par irrigations nasales (p < 0.001)*
- *Plus d'hypométabolisme chez les patients traités par ACE drugs (p = 0.032)*

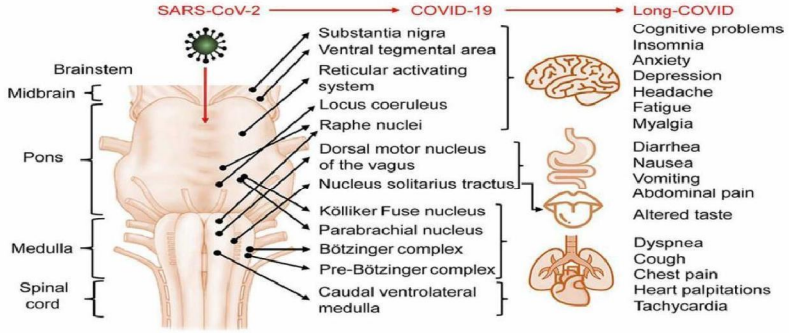
European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-021-05215-4

Persistent Brainstem Dysfunction in Long-COVID: A Hypothesis

Mechanisms of SARS-CoV-2-induced brainstem dysfunction

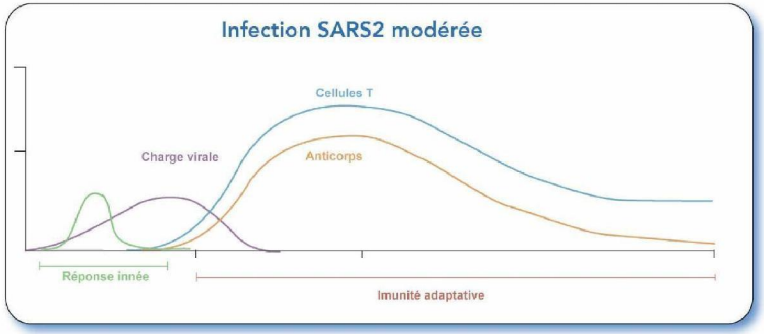


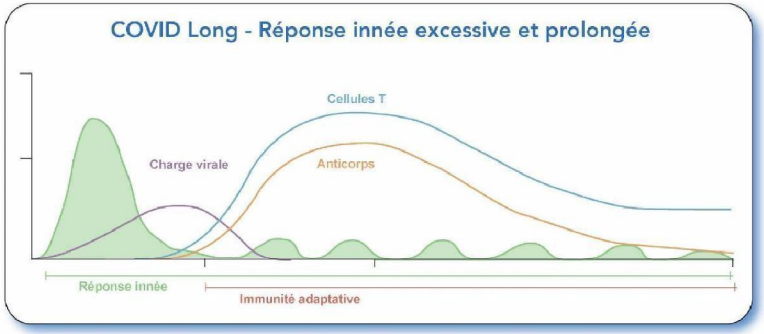
Overview of the brainstem dysfunction



Persistent Brainstem Dysfunction in Long-COVID: A Hypothesis. ACS Chem Neurosci. 2021 Feb 17;12(4):573-580.

Possible pathogenic mechanisms in Long COVID Long

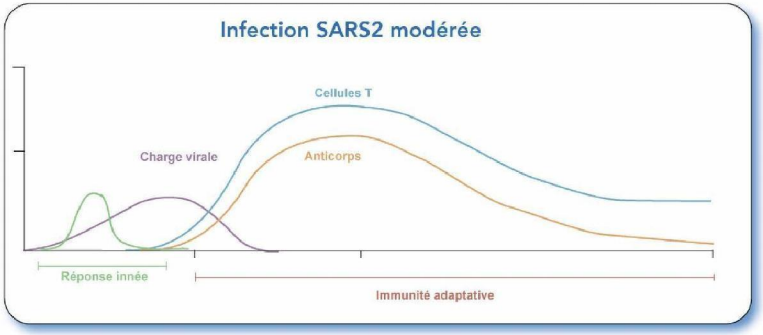


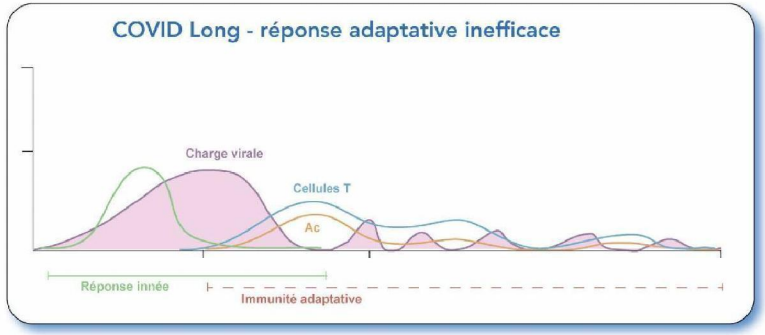


Anti inflammatory treatment?
Anti histaminic treatment?

- Chronic inflammation
- Mastocyte activation

Possible pathogenic mechanisms in Long COVID Long

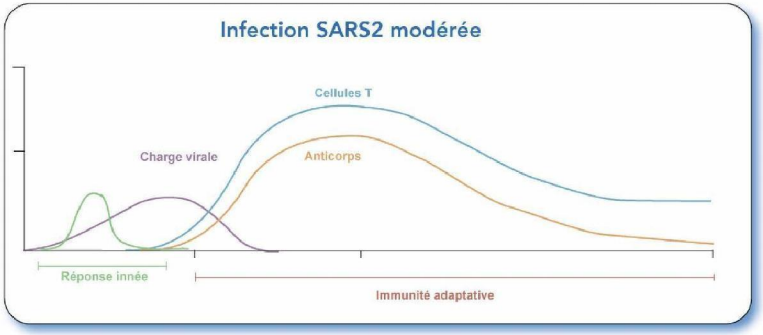


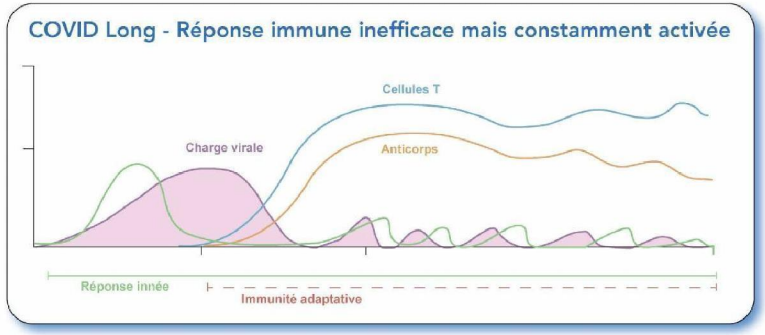


- Vaccination ?
- Antiviral treatment ?

- Weak T and B cells responses
- Viral persistence in sanctuaries
- Localized tissular damage

Possibles mécanismes pathogènes du COVID Long (4)



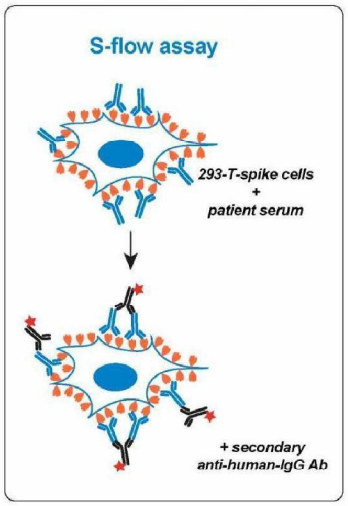


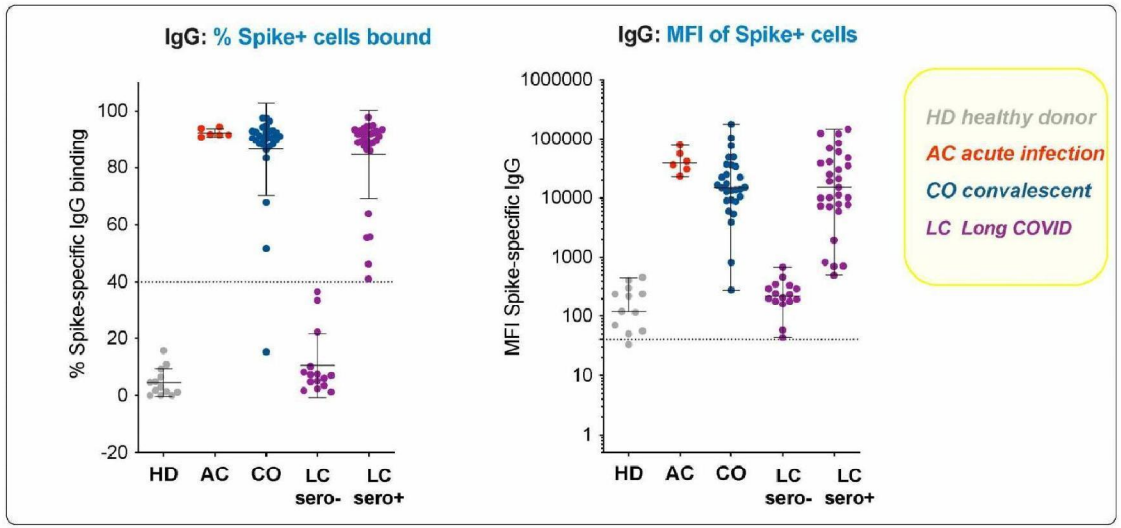
Different types of COVID Long ?Need to analyse not only the magnitude but the quality of immune responses

- Strong but inadapted adaptive immune responses
- Viral persistence in sanctuaries
- Peristent inflammation

PERSICOT study

Antibody responses in Long COVID patients





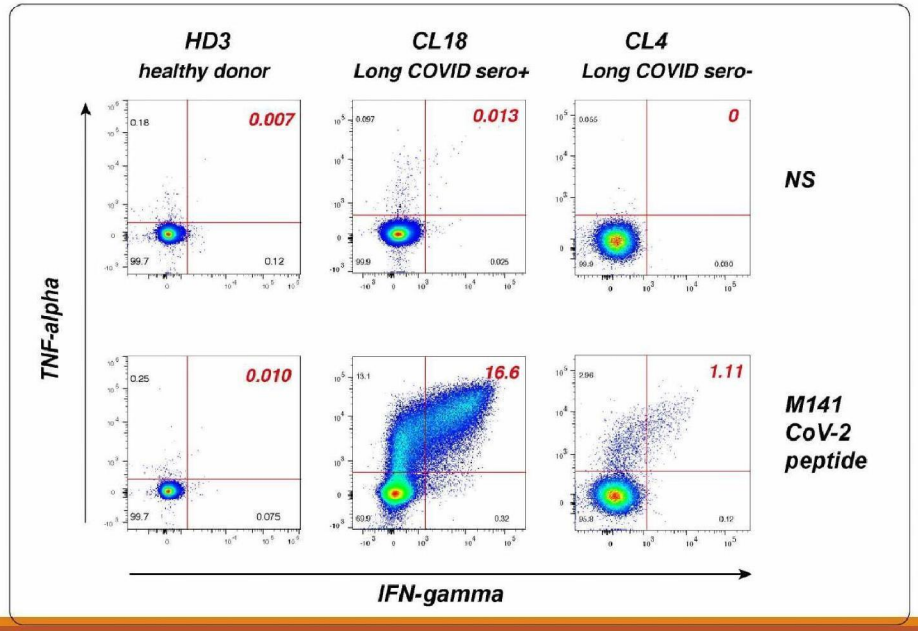
S-flow assay by 5.1.2e in O. Schwartz Unit

Antibody measurements distinguish two groups of Long COVID patients

INSTITUT PASTEUR

PERSICOT study

CD4+ T cell responses in Long COVID patients



Examples of primary CD4+ T cell line responses to a SARS-CoV-2 M peptide

- *strong response to M141 in one seropositive Long Covid patient*
- *weaker but detectable response in one seronegative Long Covid patient*

Suggests previous infection in the seronegative patient

Infect Dis Ther (2021) 10:1747–1763
https://doi.org/10.1007/s40121-021-00484-w

ORIGINAL RESEARCH

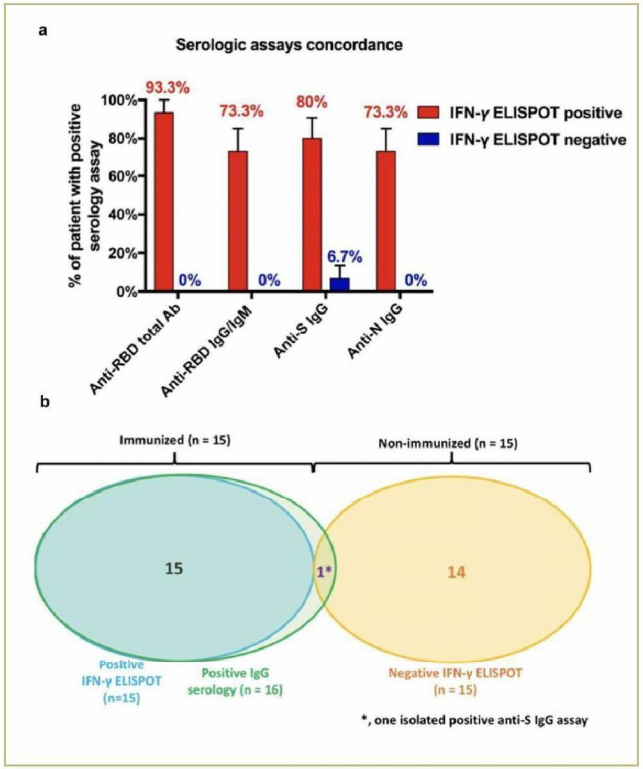
Refining "Long-COVID" by a Prospective Multimodal Evaluation of Patients with Long-Term Symptoms Attributed to SARS-CoV-2 Infection

5.1.2e

5.1.2e

Characteristics, % (*n*/*N*)	Total (*N* = 30)	Immunized (*N* = 15)	Non-immunized (*N* = 15)	Convalescent COVID-19 (*N* = 17)
Demographics				
Age (median, (IQR))	40 (35–54)	40 (31–58)	39 (35–45)	40 (31–45)
Female sex	60 (18/30)	46.7 (7/15)	73.3 (11/15)	76.4 (13/17)
Close contact with confirmed COVID-19 patients	43.3 (13/30)	46.7 (7/15)	40 (6/15)	29.4 (5/17)

- Two groups of Long COVID patients: with or without detectable adaptive responses
- No significant differences in symptoms except for higher thoracic oppression in the « non-immunized » group



Association of self-reported COVID-19 infection, SARS-CoV-2 serology results with persistent physical symptoms

The results of this study that included nearly 27,000 individuals in France and based on SARS COV 2 serology suggest that physical symptoms such as fatigue, breathlessness or impaired attention persisting 10 to 12 months after the first wave of the pandemic may be associated more with the belief in having been infected with SARS-CoV-2 than with having laboratory-confirmed COVID-19 infection.

5.1.2e *Association of Self-reported COVID-19 Infection and SARS-CoV-2 Serology Test Results With Persistent Physical Symptoms Among French Adults During the COVID-19 Pandemic. JAMA Intern Med. Published online November 08, 2021.*

Long Covid Call for Projects on effects and consequences of SARS-CoV-2 infection - 2021-2022

- Launched in collaboration with the Foundation for Medical Research (FRM) and with the support of the Ministries of Higher Education, Research and Innovation, and Solidarity and Health via CAPNET.

- Schedule: in two time sessions:
  - **Covid Long 2022-1** PAA: currently open November 8 to December 1, 2021
  - **Covid Long 2022-2** PAA: open February 1 to mid-March (exact dates TBC

In Feb 2021, the French Health Authority issued « Recommendations on prolonged forms of COVID-19 » for General Practitioners

Objective :

- Empower General Practitioners to manage in primary care patients
- Have tools to do recognize and treat patients
- Know when to send the patients to specialists

Two parts provided: a global document and technical tools

A global holistic management

The majority of patients can be managed by general practitioners : listening, empathy and a personalized approach are essential.

Regular actualizations

Réponse rapide de la Haute Autorité de Santé (HAS) : symptômes prolongés de la COVID-19: diagnostic et prise en charge. 10 Feb 2021

Back-up

Clinical assessement

- Have patients **describe their symptoms and triggering factors**
- **Eliminate** a complication of the acute phase, a comorbidity decompensation and other cause than COVID.
- **Look for**: orthostatic hypotension, O2 saturation at rest and after effort
- Make a diagnosis related to the extended phase
  - **Available scales**
  - **Parcimonious biological assessement**

Diagnoses most often made during Long COVID phase

- ✓ **Lungs**: hyperventilation syndrome, bronchial hyper reactivity
- ✓ **Cardiac**: intercostal pain, pericarditis, myocarditis, postural tachycardia
- ✓ **Neurological and ENT** : dysexecutive syndrome, cerebellar syndrome, hyposmia/phantosmia, dysautonomia (thermoregulation, gastroparesis…)
- ✓ **Digestive** : gastritis, œsophagitis, gastroparesis, motor diarrhea
- ✓ **General state** : profound fatigue, weight loss, shivering
- ✓ **Psychological**: emotional, anxiety, depressive disorders, functional diisorders.

The therapeutic strategy is based on four pillars

Symptomatic treatment

- Pains (non steroidal anti inflammatory drugs not contra-indicated)
- Gastric reflux, pericarditis, POTS...

Rehabilitation: central place

Respiratory in case of HVS. Olfactory, Otophony, sport reahabilitation – Progressive and adapted to patient possibilities

Provide all relevant information to the patiente.Teach them to manage themselves

- Know situations that trigger symptoms and limits of effort
- Continuation of physical activities even moderate (in the absence of contraindications)

Anxiety, depressive, functional disorders

- Systematic screening
- Selective serotonin reuptake inhibitors (SRNI),benzodiazepine