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Staying tuned for post-COVID-19 syndrome: looking for new research to sniff out

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Abstract. – Post-COVID-19 syndrome was defined as a persistent and protracted illness, which follows acute COVID-19 infection. This condition continues for more than 12 weeks and cannot be attributed to other clinical situations. Researchers and clinicians are allied in unraveling the molecular pathogenetic mechanisms and the clinical development of this unexpected SARS-CoV-2 infectious evolution. Anosmia, dysgeusia, fatigue, dyspnea, and 'brain fog' are common symptoms observed in the Post-COVID-19 syndrome, depicting a multiorgan involvement associated with injuries involving mainly cardiovascular, pulmonary, musculoskeletal, and neuropsychiatric systems. This commentary analyzes the state of the art of Post-COVID-19 interdisciplinary studies, confirming that we are facing a truly intricate biomedicine story.

Key Words:
Post-COVID syndrome, COVID-19, SARS-CoV-2, Neurological disease, Multiorgan disease.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the infectious agent for the current COVID-19 pandemic, that has affected >185 million people worldwide. Currently, two aspects of COVID-19 are unsolved: on the one hand the persistence and recurrence of symptoms after the acute phase, and on the other that COVID-19 is a multisystem/multiorgan disease with long-term consequences.

As people infected with SARS-CoV-2 continue to increase rapidly, also favored by the sudden expansion of viral variants, it is important to focus both on understanding the molecular mechanisms of the infection and on unveiling the potential sequelae of the Post-COVID-19 syndrome (PCS). Post-COVID-19 syndrome was defined as a condition following acute COVID-19 infection that continues for more than 12 weeks and cannot be attributed to other clinical situations[1].

As sum up by Nalbandian et al[2] the pathophysiology and organ sequelae of long COVID is under deep investigation and a wide management clinical effort is requested[2-4]. Patients with long COVID are characterized by prolonged multisystem involvement, frailty, and significant organ damage and disability.

PCS patients are affected by neurological, cardiac, and respiratory symptoms like dyspnoea, fatigue, loss of olfactory and taste function with anosmia and dysgeusia, neurocognitive problems defined as "brain fog", sleep disturbance, weakness, and chronic pain reducing physical and mental life quality[5].

Recently, Seeßle et al[6] observed in a prospective study, the persistence of neurocognitive long COVID symptoms at least for one year after COVID-19 symptom onset. Moreover, female patients were more affected compared to males, and almost half of patients showed an increase of antinuclear antibodies (ANA) correlated to neurocognitive symptoms, but unrelated to SARS-CoV-2-antibody levels. These authors suggest autoimmunity as a cofactor in etiology of long COVID[6,7].

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On the other hand, a very interesting prospective study explored for the first time, in mild COVID-19 in non-hospitalized patients, the long-term health consequences in SARS-CoV-2 convalescent patients, evidencing over 7 months of PCS. Importantly, compared to previous reports, this study underline that PCS is clinically undefined, characterized by anosmia, fatigue, ageusia, shortness of breath, and more frequently associated with lower SARS-CoV-2 IgG titers at the beginning of the observation[8].

The observation of a mild/moderate SARS-CoV-2 infection associated with an increased probability to develop a PCS syndrome, poses a very important clinical and public health issue, considering that the vast majority of people in the world have become mildly infected or even asymptomatic. Moreover, perhaps even more remarkable, it is attributable to the potential development of a pediatric Post-COVID 19 clinical picture, against which careful clinical evaluation is urgently needed[9].

Neuro-Invasion Routes

Evaluating that COVID-19 and the brain represent a large part of clinical symptomatology in affected patients and that in Post-COVID-19 syndrome, many alterations are attributable to nervous and cognitive functions, is reasonable to plan an intensive experimental effort on how neuronal damage occurs[10].

SARS-CoV-2, using the natural 'window' on the brain, enters the upper respiratory tract by air, reaches the olfactory epithelium and the first nerve endings, which 'fillet' in the lamina cribrosa towards the olfactory bulb inside of the CNS.

A hypothesis could be that the SARS-CoV-2 virus uses neuro-invasion mechanisms by 'walking' from one nerve cell to another, exploiting endogenous pathways of cellular communication between neurons in different brain areas.

Thus, it is supposable a neural olfactory route, and/or unsheathing cell route, and/or a transmucosal non-neural route[11-13].

Olfactory neurons are considered an important route to brain infection in COVID-19. Several works have demonstrated that neuro-invasion might be plausible, but definitive experimental demonstrations are lacking[12]. Importantly, in both animal and/or human studies there is no undoubted evidence of co-expression of viral proteins and/or RNA of neuronal and/or olfactory markers simultaneously[14]. The co-localization studies of viral and human neuroepithelial markers do not permit to individuate an unbiased picture of the coexistence of SARS-CoV-2 in neurons, growing the hypothesis that viral infection can be along this route retained in the brain.

The tangled network of olfactory neurons with their support cell may explain why viral proteins were observed in neurons if effectively the SARS-CoV-2 molecules are entrapped in twisted wrappings of sustentacular cells[11].

We suggest that the human olfactory epithelium has the potential to be used as a model to examine the cellular and ultrastructural state in PCS patients affected by olfactory dysfunction, as anosmia, hyposmia, dysgeusia up to the 'cognitive fog'[15].

In addition to a direct neuro-invasion, neuronal injury following tissue hypoxia or inflammation, cytokines release, and compromised blood-brain barrier integrity have been suggested as pathophysiological mechanisms underlying long-term neurological sequelae after SARS-CoV-2 infections[16,17].

More recently was evidenced that SARS-CoV-2 might infect astrocytes in the brain[18], an observation sustained by the autopsied brain from Brazilian COVID-19 patients in which a large part of infected neuronal cells was attributable to astrocytes[19]. On the other hand, Yang et al[20] demonstrated that SARS-CoV-2 molecules are lacking in the brain and choroid plexus cells, but the single cells transcriptomic analysis indicate an altered gene expression, suggesting an upregulation of inflammatory genes similarly to profiles of cognitive brain diseases, opening a new perspective on COVID-19 -related neurological disease.

Understanding the Functions of the Time Delay Relay of PCS

The state of the art on Post-COVID-19 syndrome research depicts a 'sliding doors' infective-like model, characterized by a first acute phase with the SARS-CoV-2 (*entry*), a potential development of a disease state or asymptomatic, and reappear after several weeks from remission, (*exit*). The unsolved question is that patients affected by PCS are negative to viral particles or molecules, suggesting that is sufficient for only one infection to activate a chronic mechanism that drives a multiorgan system disease onset. As consequence, this pathogenetic mechanism of SARS-CoV-2 infection open a scenario resumable with M. TVLLI CICERONIS hexameter from *DE INVENTIONE*, 'Quis, quid, ubi, quibus auxiliis, cur, quomodo, quando?':

– Who? Which molecules determined the pathological mechanisms? ***(quis)***
– What? What did it induce? ***(quid)***
– Where? Where is it located, cells, organs and tissues? ***(ubi)***
– With What? what mechanisms did it use? ***(quibus auxiliis)***
– Why? Why does this condition arise between virus and host? ***(cur)***
– What manner? How is it pathogenetic? ***(quomodo)***
– When? When does it become chronic? ***(quando)***

Last, but not least, it is conceivable to observe a Post-COVID-19 syndrome attributable to genetic variants of SARS-CoV-2 emerged and to date circulating the world?

All studies performed on PCS have been on populations affected by the variant B.1.1.7 (Alpha), B.1.351 (Beta), and shortly on B.1.617.2 (Delta). The population affected by B.1.351 SARS-CoV-2, if re-infected with B.1.617.2, will develop a Post-COVID-19 syndrome as we are studying either with a prevalence of specific neurological symptoms, rather than cardiological, or exclusively pulmonary?

Conclusions

A well-defined clinical picture of PCS is tangled and far from being understood. From the molecular mechanism of the entry of SARS-CoV-2 into cells to the enslavement of the endogenous translational machinery and biochemical mimesis in the host, from diffusion through other organs and tissues to the autoimmunity response, many pieces make up the COVID-19 puzzle are unknown[21]. We are engaged in Post-COVID-19 interdisciplinary studies from the bench to the bedside, with the aim of "sniffing" new research and unexplored therapeutic pathway.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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