

Post-Covid-19 Syndrome and Neuropsychiatric Manifestations

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One of the greatest health challenges that humanity has had to face in the last hundred years is infection by the SARS-CoV-2 coronavirus, which was first detected in December 2019 in the city of Wuhan [China] [1,2].

Coronavirus disease 2019 has become the highest priority for health systems in the years 2020-2021, due to the impact it has had on all areas of life on the planet [3], being considered the first pandemic of the 21st century [4].

According to different studies, 20 to 90% of patients who have suffered from COVID-19 present symptoms weeks or months after diagnosis of the infection [5-7].

In patients who have overcome an episode of acute COVID, the persistence of clinical symptoms beyond the time in which the acute phase of the disease is ordinarily considered to have ended is frequently observed. Different conceptual criteria have been issued in this regard [8-10].

The term prolonged COVID [Long COVID] was first used to refer to post-infection symptoms, where there were several types of evidence to demonstrate a longer and more complex disease course than that presented in the initial reports in Wuhan [11].

The researchers also initially proposed the term "post-acute COVID syndrome" as the set of signs and symptoms lasting three weeks after the onset of manifestations for the post-acute stage and "chronic COVID" to those that persist beyond 12 weeks [9].

If we take into account the clinical evolution of the infection and the replicative capacity of SARS-CoV-2, this would be a definition that can be applied in clinical practice [12].

Likewise, the United States Center for Disease Control and Prevention uses the term 'post-COVID conditions' to describe any health disorder or alteration that persists for more than four weeks after SARS-CoV-2 infection [13].

More recently, the National Institute for Health and Care Excellence [NICE] considers that the terms "chronic" or "persistent" are not appropriate and the use of "syndrome" is preferred because it reflects the "working together" of the multisystem, so proposes the following definitions [14,15]:

1. Acute COVID-19: Signs and symptoms of COVID-19 for up to four weeks.
2. Ongoing symptomatic COVID-19: signs and symptoms of COVID-19 from four to 12 weeks.

3. Post-COVID-19 syndrome: signs and symptoms that develop during or after an infection compatible with COVID-19, that persist beyond 12 weeks and are not explained by an alternative diagnosis.

Despite the fact that it seems to us the most appropriate and practical conceptualization, we are obliged to reflect on it and make some considerations, since the full spectrum of duration and severity of post-acute COVID-19 is currently unknown. However, the doctor of first contact will have to be able to recognize, document, investigate and control the symptoms, including new ones, and follow up on serious or non-serious sequelae of the disease [3].

From a clinical point of view, post-COVID sequelae vary from one patient to another, and no consensus has been reached on the characterization of possible symptoms [16], since some elements of the post-COVID syndrome, which undoubtedly exist, are not, at first glance, clearly distinguishable from that which occurs after other acute viral diseases and after prolonged stays in the Intensive Care Unit [ICU] due to diseases of a different nature. Suffice it to mention Post-viral Fatigue Syndrome and Post-Intensive Care Syndrome, with which definitive limits of differentiation could not be guaranteed [16].

In this regard, the concept of Persistent Post-COVID Syndrome [PPCS] has also been described by some authors, a recently described general term, by analogy with post-sepsis/post-ICU syndrome [17,18] that covers a set of heterogeneous symptoms for which there is no pathognomonic laboratory test, making it difficult to ignore the rising tide of physical and psychological disabilities that have been described in post-COVID patients and that have the potential to overwhelm an already overburdened Health System [19].

Several neurological and psychiatric manifestations have been reported to occur after COVID-19 [20-24].

In general, the incidences of these were higher in patients who required hospitalization, and notably in those who required ICU admission or developed encephalopathy, even after extensive hospitalization. However, the incidence and relative risk of neurological and psychiatric diagnoses were also increased even in patients with COVID-19 who did not require hospitalization. Potential mechanisms for this association include viral invasion of the Central Nervous System, hypercoagulable states, and neural effects of the immune response [25-28].

Some specific neurological diagnoses deserve individual mention. Consistent with several other reports, the risk of cerebrovascular events [ischemic stroke and intracranial hemorrhage] increased after COVID-19, and the incidence of ischemic stroke increased to nearly one in ten [or three in 100 for a first stroke] in patients with encephalopathy, in the acute phase of the disease [28,29].

Therefore, most authors agree that neurological and psychiatric morbidity is substantial during the first six months after SARS-CoV-2 infection [30].

A study published in *Lancet Psychiatry* in 2021 quantified the incidence of neurological or psychiatric complications in the following six months [45], being 33.6%, and among them, anxiety, depression, insomnia, ischemic stroke, psychosis, dementia, cerebral hemorrhage and parkinsonism. The incidence of this type of complication was higher in patients who required admission to the ICU [46.4%] or who presented encephalopathy in the acute phase, and was also higher compared to patients with influenza or other respiratory infections [31].

2.6% of patients over 65 years of age and 4.7% of those with encephalopathy were diagnosed with dementia in the first six months after suffering from COVID-19. The incidence of cognitive and psychiatric complications was also increased in patients who did not require hospital admission. Drug abuse and sleep disorders were also more frequent in the group of COVID-19 survivors [31].

Salmon-Ceron, *et al.* described fatigue in 73% of patients with post-COVID-19 syndrome and neurological symptoms in 77%, and stratified them into sensory disorders [paresthesias and neurogenic pain], headache, memory disorders and attention, anosmia/ageusia and others, such as language and thermoregulation disorders [32].

Chronic fatigue is one of the most frequent extra-respiratory symptoms of SARS-CoV-2 infection, described in 41.4% of patients included in the largest published cohorts [33,34].

All these alterations have an impact on the functional motor capacity of these patients, with reduced quality of life and return to work. Early rehabilitation, from hospital admission and especially in the most severe patients admitted to the ICU, can reduce sequelae in these patients [35].

Headache is one of the most frequent neurological manifestations, affecting 2-6% of patients who have suffered from COVID-19 [36].

Instability can be multifactorial, from vestibular involvement to subjective chronic dizziness. Asthenia is another common symptom and is associated with cognitive disorders described in the literature as “brain fog.” This has been used to define various symptoms consisting of memory impairment, naming problems, and executive impairments reported by patients [36].

The literature contains isolated cases of mononeuritis multiplex [37], Guillain-Barré syndrome [38], and meralgia paresthetica [39], and high levels of stress are common among survivors [40].

In most cases, recovery from ageusia and anosmia occurs during the first or second month, generally completely [41].

However, the data from different published studies show a fairly variable persistence time and therefore could be considered part of the post-COVID syndrome.

Psychiatric symptoms caused by SARS-CoV-2 infection may appear later and persist after infection and therefore form part of the post-COVID syndrome [42-44].

The main psychiatric manifestations related to the disease caused by SARS-CoV-2 are considered to be due to anxiety, depression, stress and sleep disturbance. [45,46].

These symptoms include, in addition to depression and anxiety, psychosis [47].

Depression, anxiety disorders, sleep abnormalities, and cognitive impairments are associated with suicidal behavior [48,49].

In the neurocognitive area, Boix highlights the decrease in concentration capacity [brain fog], memory alterations, headache and persistence of ageusia and anosmia. Anxious-depressive symptoms, as well as sleep disturbances, are very common [15].

Concentration or attention problems, memory problems, emotional lability, verbosity, euphoria, irritability, fatigue, and symptoms related to post-traumatic stress have also been described [49].

Some authors consider that health personnel who directly care for patients with COVID-19 acquire stress for fear of becoming infected and this can cause damage to their health. If the psychological adjustment mechanisms do not compensate for the situation, they may suffer from Burnout Syndrome [SBO] or post-traumatic stress disorder [PTSD], an entity that has been addressed by many authors, it has been described more frequently in nursing staff [50].

It is also described that patients with schizophrenia may have exacerbation of symptoms and patients with addiction may increase the consumption of drugs such as alcohol, cigarettes, among other harmful substances [51].

Finally, we could make some comments regarding the therapeutic approach.

A multidisciplinary approach is required in the care and follow-up of patients with Post-COVID Syndrome, as well as follow-up studies over time to elucidate the health consequences of COVID-19 [52].

There are no specific treatments available for post-COVID syndrome. Although several clinical trials are at different stages, there is currently no evidence to recommend a defined treatment [53].

If we analyze the difficulty in understanding the pathophysiology, the heterogeneity in the presentation, which in many cases is a multisystemic and multiorgan picture, with a wide spectrum of signs and symptoms, it is understood why there are so many difficulties in achieving therapeutic behavior adequate. It is recommended to prioritize the context of randomized clinical trials that allow generating knowledge to obtain results that guide us towards more specific and effective treatments.

In a generic way, behavior can be oriented through: pharmacological treatments directed at symptoms, management of nutritional deficits, physical, defective and cognitive rehabilitation, and Psychological/Psychiatric intervention [54].

In conclusion, it is important to know that patients affected by COVID-19 may present clinical manifestations after the acute phase, which make up the post-COVID syndrome, in order to develop follow-up and treatment plans for these patients.

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