

Approach to the Neuropsychiatric Sequelae of the Post-Covid-19 Syndrome

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Abstract

The SARS-CoV-2 coronavirus was first detected in December 2019 in the city of Wuhan, China, and is the seventh coronavirus known to infect humans. The disease has a wide spectrum of clinical presentation, ranging from asymptomatic to critical infection, and has become the top priority for the years 2020 - 2021. Post-acute symptoms of COVID-19 have been increasingly reported as the pandemic progresses. To date, more than 50 long-term effects have been identified, including signs, symptoms, laboratory and imaging parameters, and despite extensive work, the lasting effects of the disease have not yet been fully elucidated. This document aims to make an analytical summary of the available scientific evidence on the long-term affectation of the nervous system by SARS-CoV-2. To elaborate it, the Google Academic search engine and the descriptors COVID-19, SARS-CoV-2, neuropsychiatric manifestations/ complications and post-covid-19 syndrome were used. The Medline, Scielo, Scopus and Medscape databases were used. The definitions described for the Post-Covid Syndrome were reviewed, as well as the general clinical aspects, neuropsychiatric aspects and the general therapeutic approach. It is concluded that 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.

Keywords: SARS-Cov-2 Coronavirus; Post-Covid-19 Syndrome; Neuropsychiatric Aspects; Therapeutic Approach

Introduction

The SARS-CoV-2 coronavirus was first detected in December 2019 in the city of Wuhan (China) and is the seventh coronavirus known to infect humans, after the identification of the SARS virus and the Middle East respiratory syndrome virus. Middle this century. The rapid increase in infected patients around the world represents one of the greatest health challenges that humanity has had to face in the last hundred years [1].

Coronavirus disease 2019 (COVID-19) has a wide spectrum of clinical presentation, ranging from the asymptomatic form to a critical infection and has become the highest priority for the years 2020-2021, due to the impact it has had in all areas of life on the planet [2], considering it the first pandemic of the 21st century [4].

Post-acute symptoms of COVID-19 have been increasingly reported as the pandemic progresses. To date, more than 50 long-term effects have been identified, including signs, symptoms, laboratory and imaging parameters, and despite extensive work by the scientific community, the lasting effects of the disease have not yet been fully elucidated [3].

Long-term clinical manifestations of COVID-19 can occur in young patients as well as in patients with advanced disease and in those with or without a history of comorbidities [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. The figures may be higher if the follow-up is done on patients who required hospitalization and, therefore, with more severe initial symptoms [5].

It should be borne in mind that various infectious diseases can cause a wide variety of chronic symptoms and clinical sequelae of multiple organ dysfunction have been described in survivors of SARS-CoV and Middle East respiratory syndrome-associated coronavirus (MERS-CoV) from previous pandemics [6].

However, there is also no consensus from the conceptual point of view, which can lead to inadequate interpretations and, therefore, to management, which is the most worrying.

This document aims to make an analytical summary of the available scientific evidence on the long-term affectation of the nervous system by SARS-CoV-2. To elaborate it, the Google Academic search engine and the descriptors COVID-19, SARS-CoV-2, neuropsychiatric manifestations/complications and post-covid-19 syndrome were used. The Medline, Scielo, Scopus and Medscape databases were used.

Conceptual considerations

The post-COVID-19 syndrome is not a homogeneous or unique entity, and a great variation in estimates of its incidence, prevalence and clinical presentation has been described [6].

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 [7].

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 [8].

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 [10].

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 [10].

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 [11,12]:

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.

Although it seems to be the most appropriate and practical conceptualization, not all researchers share it.

That is why we are obliged to reflect on it and make some considerations.

Currently, by consensus, the full spectrum of duration and severity of post-acute COVID-19 is unknown. However, it is expected, in turn, that many patients with prolonged COVID-19 will recover without the help of a specialist doctor; however, the first contact physician will have to be trained to recognize, document, investigate and control the symptoms, including new ones, and follow up on serious or non-serious sequelae of the disease [2].

General clinical aspects

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 [13], 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. This is an important element to take into consideration. Suffice it to mention Post-viral Fatigue Syndrome and Post-Intensive Care Syndrome with which definitive differentiation limits could not be guaranteed [13].

In general, long-term symptoms seem to be more frequent in patients with a severe initial disease, however, they have also been observed in people with a mild infection, who did not require hospitalization and even in young adults and children without chronic underlying diseases. existing [14].

Post-ICU syndrome (PICS) is a clinical entity that affects a significant number of critically ill patients (30 - 50%). It is characterized by physical sequelae (mainly respiratory and neuromuscular), cognitive (alterations in memory and attention) and psychic (depression, anxiety, stress and/or post-traumatic stress syndrome) on discharge from the ICU, which persist in the long term and negatively impact the quality of life of patients and their families [15].

Persistent Post-COVID Syndrome (PPCS), a recently described general term, has also been terminologically described by some authors by analogy with post-sepsis/post-ICU syndrome [16] which covers a set of heterogeneous symptoms for 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 [17].

Neuropsychiatric manifestations.

Several adverse neurological and psychiatric manifestations occurring after COVID-19 have been predicted and reported [18].

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 [19].

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 [19].

The expression of ACE-2 in the endothelial cells of the brain allows the virus to directly damage the blood-brain barrier (BBB), the inflammatory response can also cause changes in the function of said barrier, in addition, SARS-CoV-2 can enter in the brain by transsynaptic transfer through the optic and olfactory nerve channels [20].

Therefore, most authors agree that neurological and psychiatric morbidity is substantial during the first six months after SARS-CoV-2 infection [6].

A study published in the *Lancet Psychiatry* in 2021 retrospectively analyzed a cohort of 236,379 COVID-19 survivors and a control group of patients who had influenza or another type of respiratory infection, but did not have COVID-19, and quantified the incidence of neurological complications or psychiatric in the following six months [21].

The incidence of complications in the group with COVID-19 was 33.6%, and among them, anxiety (17.4%), depression (13.7%), insomnia (5.4%) stands out, ischemic stroke (2.1%), psychosis (1.4%), dementia (0.67%), cerebral hemorrhage (0.56%) and parkinsonism (0.11%). 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 [21].

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 [21].

It must be taken into account that cerebrovascular complications, encephalopathy and neuroinflammatory syndromes are more frequent in the acute phase, although sequelae persist for months. In contrast, symptoms such as chronic fatigue, headache, memory, attention and executive function problems are relatively common in the post-COVID-19 syndrome [6].

Salmon-Ceron, *et al* described fatigue in 73% of patients with post-COVID-19 syndrome and an aggregate of neurological symptoms in 77%, and stratified them into sensory disorders (paresthesias and neurogenic pain; 56%), headache (41%), memory and attention disorders (37%), anosmia/ageusia (30%) and others (24%), such as language and thermoregulation disorders [22].

The most frequent symptomatology, fatigue as the most characteristic symptom (present in 60-70%), defined as intense tiredness that interferes with activities of daily living [23].

Persistent muscle fatigue and weakness is one of the most common symptoms of post-COVID syndrome [24].

Chronic fatigue is the most frequently described symptom and often occurs in the absence of objective abnormalities of respiratory function or pulmonary fibrosing lesions [6].

It shares features with chronic fatigue syndrome described after other infections, including SARS-CoV-1, MERS, and community-acquired pneumonia [25].

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. Regarding persistent fatigue, the data published in two studies suggest a frequency of 35 - 53% at 4 - 8 weeks post-infection, and 16% at 12 weeks post-infection [5,26].

All these alterations have an impact on the functional motor capacity of these patients, with reduced quality of life and return to work (only 40% 2 - 3 months after the acute episode have returned to work). Early rehabilitation, from hospital admission and especially in the most severe patients admitted to the ICU, can reduce sequelae in these patients [27].

Among the neurological manifestations, some authors frequently highlight headache, dizziness, asthenia, anosmia and cognitive alterations [28].

Headache is one of the most frequent, affecting 2-6% of patients who have suffered from COVID-19. It is suggested that it could be similar to chronic persistent headache de novo. It is a continuous, holocranial headache and is not usually accompanied by nausea, vomiting, phonophobia or photophobia [29].

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 [29].

The literature contains isolated cases of mononeuritis multiplex [30], Guillain-Barré syndrome [31], meralgia paresthetica [32], and high levels of stress are common among survivors [33].

In most cases, recovery from ageusia and anosmia occurs during the first or second month, generally completely [34].

However, the data from different published studies show a quite variable persistence time: 17 - 56% at 4 weeks, 10 - 23% at 8 weeks, and 4 - 46% at 12 weeks [35] 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 [36].

Persistent psychiatric disorders among COVID-19 survivors may be related to psychological factors and neurobiological injury. In many cases, it is probably difficult to separate the impact of psychological factors from neurobiological effects [37].

In the SARS-CoV-1 (2002) and MERS-CoV (2012) epidemics, psychiatric sequelae were observed. Up to a third of post-SARS patients presented anxious and depressive symptoms a year after passing the infection. The post-SARS chronic syndrome was even described, which included symptoms such as myalgia, asthenia, sleep disturbance and depression, some time after the episode, similar to chronic fatigue syndrome [38].

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 [39].

Depression, anxiety disorders, PTSD, sleep abnormalities, and cognitive impairments are associated with suicidal behavior [40].

Likewise, neuropsychiatric symptoms have also been reported after SARS-CoV-2 infection [41].

These symptoms include, in addition to depression and anxiety, psychosis [42].

This has been reported in some series and, in fact, the first Cuban patient diagnosed with a psychotic disorder after COVID-19 infection has already been described [43].

In the neurocognitive area, Boix highlights the decrease in concentration capacity (brain fog), memory alterations, headache and persistence of ageusia and anosmia. Anxiety-depressive symptoms, as well as sleep disturbances, are very common [12].

Concentration or attention problems, memory problems, emotional lability, verbosity, euphoria, irritability, fatigue, and symptoms related to post-traumatic stress have also been described [44].

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 [45].

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 [46].

In a study conducted in the United Kingdom by Varatharaj, *et al.* a 23% frequency of Delirium was found in the study population (124 patients with COVID-19) [47].

Another study in Italy, by Liguori C., *et al.* with a sample of 103 patients, found that 23 (22.3%) of them presented confusional syndrome [48].

It is important to point out that the persistence of any of the aforementioned findings makes it necessary to rule out other causes that are more likely than post-COVID syndrome. Only the exclusion of other causes, treatable or not, would allow these manifestations to be attributed to the syndrome we are discussing.

Musculoskeletal manifestations

The most common musculoskeletal manifestations in patients after COVID-19 are arthralgia, myalgia, muscle cramps and contractures, back pain, and muscle atrophy and weakness.

Muscle pain or myalgia are a frequent cause of medical consultation. They can affect one or several muscles of the body and in most cases they are benign and self-limited. Ligaments, tendons, and fascia may also be involved. The causes that provoke them are very diverse.

In large series, myalgias are part of SARS-CoV-2 infection in 20% of cases. Regarding persistent muscle pain, only the study by Carfi, *et al.* 37 reports that the symptom remained in 6% of the cases at 8 weeks from the diagnosis of the infection [5].

Therapeutic approach

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

Post-COVID-19 'recovery' cannot be based solely on a negative PCR or hospital discharge. There is a marked variation in the duration, severity, and fluctuation of symptoms, which can affect survivors' quality of life, functional status, cognition, and mood, leading to severe disability [6].

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 [49].

There are no specific treatments available for post-COVID syndrome. Although various clinical trials are at different stages, there is currently no evidence to recommend a defined treatment [49].

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 [50].

Conclusión

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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