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Non-Pulmonary Features of Long Covid-19 Syndrome: Psychiatric Symptoms and Disorders

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Abstract

After respiratory disorders, psychiatric consequences are the most frequent components of the post-COVID-19 syndrome. Psychiatric disorders have been less frequently reported because their diagnosis is more difficult to establish. This article tries to address the same.

Keywords: *Non-pulmonary, Long Covid-19.*

Prevalence

After respiratory disorders, psychiatric consequences are the most frequent components of the post-COVID-19 syndrome. Understandably, COVID-19 might generate acute psychiatric consequences and symptoms may persist over time after the acute phase. The anxiety-provoking social and media context, the fear of a serious form of the disease, the fear of not being able to benefit from appropriate care, especially in the first weeks of the pandemic, the lack of established curative treatment, the lack of visits from relatives for hospitalized patients, brain damage caused by the virus itself, and inflammatory and immune imbalance have favored anxiety or depressive symptoms. The traumatic experiences of the acute disease and care, sometimes in degraded conditions, may have favored the onset of post-traumatic stress. Finally, the persistence of physical disorders for weeks or months after the acute episode may have contributed to psychiatric symptoms and disorder prevalence. What is it truly?

Importantly, symptoms, as assessed using simple questionnaires, and disorders, whose diagnosis requires supervised psychiatric interviews, must be distinguished. The prevalence of psychiatric symptoms in the months following COVID-19 has been reported in several studies based on self-report questionnaires, which provided follow-up for 14 days to 6 months. They consistently reported a high prevalence of insomnia (31–54%), anxiety symptoms (5–46%), depressive symptoms (9–42%), and post-traumatic stress symptoms (10–57%) (supplementary table S1) [7, 8, 12, 48–69]. In the COMEBAC study cohort, we reported insomnia in 54% of patients, anxiety symptoms in 31%, depressive symptoms in 22%, and post-traumatic stress symptoms in 14% at 4 months after hospitalization for COVID-19 [7].

Psychiatric disorders have been less frequently reported because their diagnosis is more difficult to establish. A recent review and meta-analysis estimated that 53 million additional major depressive disorders and 76 million additional anxiety disorders are related to the pandemic worldwide since the beginning of 2020 [70]. Two Italian studies reported a systematic evaluation by qualified psychiatrists of patients after the acute episode of COVID-19 [55, 71]. One study reported the onset of a new mental disorder within 3 months of the acute episode in 12% of patients [71]. In the other study, the prevalence of post-traumatic stress disorder was 30% at 1–3 months after a severe acute episode [55]. However, these studies did not compare these prevalence rates to populations with conditions other than COVID-19.

Two studies performed by TAQUET and co-workers [72, 73] compared psychiatric disorders in patients with and without COVID-19 from very large cohorts (236379 and 62354 COVID-19 survivors) based on electronic medical reports. The incidence of mental disorders was higher in patients with COVID-19 than

in other populations (influenza, other respiratory infections, skin infections, cholelithiasis, urolithiasis, or large bone fractures) [72, 73]. In one of the studies, an anxiety disorder appeared in 7% of patients 6 months after COVID-19 and a mood disorder was observed in 4% [72].

Risk factors

What are the risk factors for presenting persisting psychiatric symptoms or disorders? Typical of psychiatric symptoms and disorders, the female sex is associated with higher levels of anxiety, depressive and post-traumatic stress symptoms [49], and disorders [71]. In one study, patients with post-traumatic stress disorder had a more frequent psychiatric history [71]. In another study, younger patients had higher levels of depression and sleep disturbances 1 month after COVID-19 than older patients [49].

Intuitively, psychiatric disorders should be expected in patients with the most severe forms of acute COVID-19. However, no convergent evidence has emerged regarding the association between the prevalence of symptoms or disorders and COVID-19 severity. In one of the large cohorts based on electronic health records, the incidence of these disorders was higher in patients who presented with a severe form of the disease (hospitalization, admission to ICU, and acute encephalopathy) [72]. MAZZA et al. [49] showed that a higher systemic immune-inflammatory index (platelets×neutrophils/lymphocytes) during acute COVID-19 was associated with anxiety and depression symptoms after 1 month and depressive symptoms after 3 months. However, RAMAN et al. [62] did not replicate these findings. In one of the largest cohorts of COVID-19 survivors published to date, HUANG et al. [12] reported that psychiatric symptoms were associated with the most severe cases of acute COVID-19 (i.e., high-flow nasal cannula or mechanical ventilation) but not with oxygen dependence. However, this association has not been observed in several other studies [53, 58, 62, 63], including for patients requiring intensive care [12, 63].

Interaction with other post-COVID-19 symptoms

Interestingly, anxiety, depression, and post-traumatic stress symptoms have been associated with concomitant dyspnoea in the months following acute COVID-19 [51, 62, 65]. An association of asthenia with gastrointestinal symptoms and cognitive disorders has also been reported [51]. In contrast, no association was observed between neurological symptoms during acute COVID-19 and psychiatric symptoms 6 months later [74]. In another study, patients with post-traumatic stress disorder had more physical symptoms persisting 3 months after the acute infection [71]. A recent study using electronic health records found that psychiatric disorders diagnosed after acute COVID-19 co-occurred more frequently with non-psychiatric symptoms than after influenza [75].

Altogether, the association between COVID-19 acute severity and subsequent psychiatric symptoms remains unclear. The results from well-designed perspective cohort studies are needed.

Cognitive consequences

Symptoms and frequency

During the acute phase of COVID-19, clinical evidence of neurological manifestations of the infection exists. “Impaired consciousness” with somnolence, delirium [76], encephalomyopathy [77], meningitis [78], and strokes [79–81] have been reported as “neuro-COVID” manifestations. Brain MRI has been described as abnormal in up to 56% of these patients and a variety of lesions, including ischaemic strokes, leptomeningeal enhancement, and encephalitis, have been observed.

In the post-COVID-19 phase, the issue of neurological sequelae (or de novo manifestations) of the infection has rapidly emerged. In addition to persistent central nervous system (CNS) impairment in patients with strokes or documented encephalopathy beginning in the acute phase, evidence for cognitive dysfunction in patients without acute neuro-COVID-19 and/or with normal brain imaging is increasing. Cognitive complaints have been reported in several studies within 4–5 months after acute COVID-19, with marked similarities among countries impacted by the pandemic. These findings were observed by authors from New York (using the OASIS-D1 mandatory assessment tool) [82], the Netherlands (Cognitive Failure Questionnaire) [53, 58], Italy (self-report questionnaire or Mini-Mental State Examination evaluation) [4, 51], France (self-report questionnaire) [83], Germany (Telephone Assessment of Cognitive Status (TICS)) [84], Spain (complete neuropsychological battery) [85], the UK (Montreal Cognitive Assessment) [62], Bangladesh (telephone assessment) [86], Brazil (TICS) [87] and China (complete neuropsychological battery) [88]. One difficulty is the heterogeneity in reporting these outcomes without standardized evaluations. Most studies report the use of screening tools such as the

Montreal Cognitive Assessment and the Mini-Mental State Examination for a telephone assessment of cognitive complaints. Interestingly, although most of these studies evaluated patients after hospital discharge for COVID-19, some included outpatients with similar cognitive complaints [58].

However, a precise estimation of the exact prevalence of cognitive sequelae is difficult due to the limitations of most of these studies. Many included a limited number of patients, used only self-administered questionnaires, or did not include a control population. The population included was sometimes heterogeneous (hospitalized or non-hospitalized patients in the acute phase, the initial diagnosis of COVID-19 with or without a positive PCR test).

When considering only the objective cognitive evaluation, a reduced performance has been globally reported in 15–40% of patients. One of the first extended reports on cognitive impairment was published by ALMERIA et al. [85]. They reported on 35 patients from Spain without any prior psychiatric or cognitive history within 35 days after hospital discharge in the first wave of the pandemic during the spring of 2020. All patients underwent a large neuropsychological battery of tests evaluating verbal, visual, and working memory, memory coding, attention, process speed, and executive function. Overall, 34% of patients had cognitive complaints, which were notably not associated with cognitive performance. Patients with complaints recorded significantly worse scores on anxiety and depression tests, emphasizing the link between cognitive and psychiatric symptoms. Cognitive impairment was associated with headache, anosmia, oxygen therapy during the acute phase, and diarrhea, suggesting roles for severe initial manifestations and persistent symptoms in neuropsychological performance. Reduced sustained attention, executive function, visuospatial processing, and memory have been reported compared with controls [84, 85, 89]. SOLDATI et al. [87] reported that 13% of patients who recovered from COVID-19 met the criteria for mild cognitive impairment, as observed in patients with other viral infections such as HIV. Notably, some studies enrolled patients with prior alterations in mental health [87], but some studies excluded these patients [85], once again limiting the extrapolation of the conclusions.

Putative mechanisms

Neurological symptoms and cognitive dysfunction might result from virus-related CNS damage and/or non-CNS systemic manifestations such as hypoxia or inflammation [90]. Human coronaviruses are considered potentially neurotrophic. As with severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), the virus might directly infect neurons, especially in the olfactory area, through interaction with ACE2 and then be transported through the axons to the CNS [91]. The temporal region and the hippocampal area seem to be specifically vulnerable in animal models of coronavirus infections [92], as observed in non-coronavirus respiratory infections such as influenza [93] and might be responsible for part of the cognitive dysfunction.

Another indirect role for virus-related CNS dysfunction might be inflammation. Elevated levels of pro-inflammatory cytokines produced during acute COVID-19 can cross the blood-brain barrier and activate astrocytes and microglial cells. They in turn induce the release of interleukin-1β, whose receptors are widely expressed on hippocampal neurons. Additionally, SARS-CoV-2 may decrease ACE2-mediated brain-derived neurotrophic factor activity, which theoretically prevents excessive microglial activation and neuronal inflammation. Lastly, elevated levels of serum markers of axonal injury (neurofilament light chain protein) and astrocytic activation (glial fibrillary acidic protein) have been detected in patients with COVID-19, indicating potential CNS damage during the acute phase that might persist in the aftermath of the infection [94, 95].

Finally, other interrelated factors, such as the severity of the initial infection, might account for some of the symptoms or sequelae. Indeed, profound hypoxemia and mechanical ventilation [96] or extracorporeal membrane oxygenation procedures for patients admitted to the ICU might be associated with persistent cognitive dysfunction and psychological disturbances in the long term, which are perhaps associated with a risk of cerebral atrophy and ventricular enlargement. The role of the systemic manifestations and the management of long-term CNS consequences of COVID-19 remains to be investigated.

Cardiac consequences

Acute cardiac injury during COVID-19

In contrast to cognitive or psychiatric consequences, post-COVID-19 cardiac symptoms always result from sequelae of acute cardiac injury [97]. Indeed, in the acute phase of COVID-19, cardiovascular involvement is one of the first manifestations of infection [98]. SARS-CoV-2 affects the

cardiovascular system through several mechanisms [99]: invasion of cardiomyocytes by the virus via ACE2, major systemic inflammation, vascular thrombosis associated with hypercoagulability [100], myocardial ischemia resulting from the destabilization of coronary plaques, hypoxemia and stress cardiopathy [99].

However, the incidence and nature of acute cardiovascular manifestations of COVID-19 are highly variable, ranging from an asymptomatic troponin elevation to fulminant myocarditis resulting in cardiogenic shock [98]. The elevation of troponin levels is found in 20% of patients [101], but it is non-specific since it may result from myocardial ischemia, myocarditis, pulmonary embolism, or renal failure. Moreover, increased troponin levels were reported in a similar proportion in patients with ARDS associated or not with COVID-19 [102]. Cardiac arrhythmias have been reported in 7% of 393 hospitalized patients (and up to 19% of those who were mechanically ventilated) [103].

Long-term consequences

Based on the variability in the type and incidence of acute COVID-19 cardiac symptoms, the finding that long-term sequelae remain largely imprecise is not surprising. Palpitations and chest pain were reported in 9% and 5% of patients, respectively, evaluated at 6 months in a Chinese study [12], but they are of course not specific to any lesions. In the COMEBAC cohort of patients, a left ventricular ejection fraction (LVEF) <50>

Several studies, all the relatively small size, reported a cardiac MRI evaluation of the myocardium in patients recovering from COVID-19 [108–111]. They showed the existence of myocardial edema, necrosis, and fibrosis, which are probably sequelae of previous myocarditis. Approximately 40% of these abnormalities were not related to myocardial ischemia [112]. The incidence of these anomalies varies, ranging from 60% [108] to 30% [109, 110] of the patients studied at 3–4 months following the initial attack. These abnormalities may be present in patients who do not experience acute cardiac manifestations [108]. However, the clinical consequences of these abnormalities are unknown.

In summary, while some patients certainly experience persistent cardiovascular abnormalities 3–6 months after the initial COVID-19-episode, large-scale studies that describe the exact incidence, consequences, risk factors, and late evolution of these attacks are lacking.

Olfactory and taste disorders

Acute symptoms

During the first COVID-19 wave, a substantial increase in olfactory and taste disorders (OTD, i.e. anosmia, hyposmia, and ageusia) was observed and was mainly reported in SARS-CoV-2-infected patients [113]. OTD was thus considered a major diagnostic criterion for COVID-19 [114]. In patients with mild COVID-19, the estimated OTD prevalence ranges from 56.5% to 85.9%, according to the OTD evaluation method [115]. The exact pathophysiology of OTD in patients with COVID-19 remains to be elucidated, but local mucosal inflammation and olfactory epithelial destruction appear to be the main mechanisms [116, 117]. Conversely, COVID-19 only appears to exert a limited effect on olfactory nerves and cerebral areas, at least during the acute phase [118].

Long-term sequelae

OTD long-term follow-up in patients with COVID-19 was studied in several cohorts and predictive factors of smell recovery remain to be identified [119]. In a large European study, 1363 patients with COVID-19 experiencing OTD were asked to report their olfactory function after OTD onset. At 2 and 6 months, 75% and 95% of patients recovered olfaction, respectively. A poor prognosis for olfactory recovery was statistically related to the severity of the baseline olfactory objective evaluation [120]. Smaller studies reported a similar prevalence, although higher rates have been reported in hospitalized patients [121, 122].

Endocrine sequelae

Based on the known presence of coronaviruses in several endocrine glands [123], and ACE2 expression observed in the human hypothalamus, pituitary, thyroid, gonads, and pancreatic islets [124], researchers have hypothesized that SARS-CoV-2 might affect the endocrine system. Nevertheless, evidence that endocrine disorders may belong to the post-COVID-19 syndrome is unclear.

The most obvious consequences of COVID-19 are glucometabolic control. Indeed, several arguments suggest the involvement of SARS-CoV-2 in the occurrence of abnormalities in glucose metabolism [125–127]. New-onset hyperglycemia, insulin resistance, and β-cell hyperstimulation have been reported in one study of patients with COVID-19 without a history of diabetes [128]. In this study, among patients with new-onset hyperglycemia at hospital admission for COVID-19, ~35% of patients had persistent hyperglycemia in the next 6 months and overt diabetes was diagnosed in ~2% of patients. Interestingly, continuous glucose monitoring of

normoglycemic patients who recovered from COVID-19 showed a greater duration of glycemia characterized by a glucose concentration >140mg·dL−1, higher mean postprandial glycemia at 120 min, and higher mean blood glucose and higher nadir blood glucose levels compared with healthy controls [128]. Therefore, fasting plasma glucose and hemoglobin A1c levels should be monitored for at least several months after COVID-19 recovery, even in patients without a history of diabetes.

Alterations in thyroid function have been described in the acute phase of COVID-19 with contradictory observations. Overt and subclinical thyrotoxicosis have been reported, mostly due to subacute thyroiditis [129–131]. In a few cases, a clear autoimmune etiology was found [132]. A non-thyroidal illness pattern characterized by low thyroid-stimulating hormone (TSH), thyroxine, and triiodothyronine levels has also been observed [132, 133]. However, to date, data on thyroid function after COVID-19 recovery are not consistent. In the few studies reporting follow-up (up to 2–3 months), TSH levels had returned to baseline [7, 129, 130, 132].

Currently, no reports of a clear effect of SARS-CoV-2 on the pituitary are available. Corticotropic insufficiency has been hypothesized due to the use of high doses of corticosteroids in the acute phase of COVID-19 and might participate in the fatigue observed in patients with long COVID-19. However, a recent study, in which adrenal function was evaluated with a short Synacthen test (250 µg intravenous bolus), showed no difference in baseline or peak cortisol after Synacthen according to disease severity or history of corticosteroid treatment [134]. Cortisol values and thyroid function tests in this study were not different between patients with persistent fatigue and those without. Finally, since the presence of ACE2 receptors has been reported in the testicles, the effect of SARS-CoV-2 on gonadal function should be evaluated [135].

Miscellaneous

In addition to the currently well-described cardiorespiratory, cognitive, or psychiatric manifestations of post-acute COVID, various other clinical manifestations have been described, some persisting symptoms of the acute phase and some other new-onset symptoms. Their mechanisms remain to be determined.

General asthenia may be the most frequent symptom reported by patients after the initial infection. In all the reported series analyzing fatigue in the 6 months of the post-acute phase, fatigue has been reported in 40–70% of patients [6, 7, 12, 83, 136, 137]. This evaluation depends on the tool used to evaluate asthenia (e.g., EuroQol EQ-5D-5L in the articles by DAHER et al. [136], GARRIGUES et al. [83] and HUANG et al. [12], Chalder Fatigue Scale used by TOWNSEND et al. [137], and Modified Fatigue Inventory used in the COMEBACK study series [7]). Reasons for persistent fatigue certainly arise from multiple origins. GHOSN et al. [6] reported data from a large French series and described persistent symptoms at 3- and 6-months post-infection. The persistence of symptoms (including fatigue) was associated with female sex, ICU management, and several symptoms at admission. However, other studies have reported that both patients with severe and non-severe diseases during acute infection may experience persistent fatigue after 6 months [137]. Overall, fatigue is associated with the impaired perception of quality of life, as we and others have reported, as well as with persistent dyspnoea, cognitive complaints, and psychiatric symptoms [138].

However, fatigue might be included in a post-infective fatigue syndrome, as already described for herpesviruses [139]. Many viruses (especially Epstein–Barr virus and cytomegalovirus) have been implicated in the emergence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [140, 141]. It has also been described in patients with MERS-CoV infection [142] and SARS-CoV infection [143, 144]. ME/CFS is a poorly understood multisystem disorder that includes severe fatigue, post-exertion malaises, and pain, with substantial reductions in the functional activity and quality of life. This disorder might explain some symptoms observed after SARS-CoV-2 infection, such as muscle weakness, diffuse pain, myalgia, and joint pain, which are reported to various extents in multiple published series [145, 146]. Other functional symptoms, such as urticaria/pruritus, persistent diarrhea, or weight loss, have also been described. These often-non-specific symptoms have all been described during post-infective ME/CFS [140].

One major difficulty is that the main hypothesis is lacking to explain these various symptoms. Putative explanations are questioned, such as viral protein persistence in epithelial reservoirs [114], autoimmunity [147], low-level inflammation (as observed in ME/CFS [148]), mitochondrial dysfunction [149] or virus-induced dysautonomia [150], which only partially explain cardiopulmonary deconditioning and persistent dyspnea. Overall, better knowledge of these persistent symptoms is needed for both physicians and patients to improve

care.

Conclusions

The COVID-19 outbreak has been a major challenge for health systems worldwide, requiring the complete mobilization of health resources. As a result of the successive COVID-19 waves, chronic complications of SARS-CoV-2 infection emerged that were grouped under the term “post-acute COVID-19 syndrome” or “long COVID-19”. Patients with post-acute COVID-19 syndrome experience multifactorial dyspnoea and multiple organ involvement, usually with overlapping symptoms, leading to a substantial effect on their quality of life (figure 3). Notably, these chronic symptoms are not intimately related to the initial severity of COVID-19 and some of them might be included in a multisystem disorder such as CFS. Given the millions of patients infected with SARS-CoV-2 worldwide and the need for multidisciplinary management of these chronic complications, post-acute COVID-19 syndrome will be a major issue for various healthcare providers in the coming months. Based on the literature and the experience of the COMEBAC study [7], in figure 4 we propose a multidisciplinary screening and follow-up algorithm for patients after COVID-19, based on questionnaires 4–6 months, possibly during a telephone or remote consultation, and then according to the symptoms and severity of the initial COVID-19, an ambulatory multidisciplinary consultation with respiratory, neuropsychological, and symptom-oriented assessment. International collaborations are needed to better define the pathophysiology, prevalence, effects of treatments, and long-term evolution (after 12 months) of post-acute COVID-19 syndrome.

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