Frequent Psychiatric and Neuropsychiatric Symptoms of Post-COVID-19 Syndrome

Subjects: Health Care Sciences & Services | Neurosciences
Contributor: Lamyae Benzakour, Guido Bondolfi

The World Health Organization (WHO) has defined a post-COVID-19 condition. Some of these symptoms can be categorized as psychiatric and neuropsychiatric post COVID-19 symptoms if they appeared in the aftermath of COVID-19, including depression, anxiety, post-traumatic stress disorder, somatic symptoms disorders such as hyperventilation syndrome, fatigue, cognitive and sleep disorders. Psychiatric and neuropsychiatric post-COVID-19 present mental health specialists with difficult challenges because of its complexity and the multiple ways in which it integrates into a singular somatic context.

Keywords: COVID-19 ; psychiatric ; post-COVID-19 syndrome ; treatments ; psychotherapy

1. Introduction

The clinical entity long COVID-19 made its initial appearance in the spring of 2020. At this time, many patients reported it on social media. The first standardized medical definition was suggested for symptoms in infected patients who did not recover for several weeks or months following the onset of COVID-19 [1]. Several medical and scientific definitions were then proposed. For instance, one from the American National Institutes of Health included a temporal limit, considering long COVID-19 to occur in patients who have symptoms four weeks after the onset of symptoms of COVID-19, as confirmed by positive test results for SARS-CoV-2, or who have symptoms suggestive of COVID-19 without a test [2]. More than four weeks after the onset of symptoms, around one-third of outpatients present persistent symptoms, mainly fatigue, dyspnea, and loss of taste or smell [3]. Numerous symptom clusters have been identified in COVID-19 [3], including the following: general (mainly fatigue); respiratory (cough, breathlessness, chest pain); cardiovascular (e.g., myocarditis, pericarditis, postural orthostatic tachycardia syndrome) [4]; ear, nose, and throat (anosmia, ageusia); pain (headache, myalgia, arthralgia); and psyciatric and neuropsychiatric symptoms (e.g., “brain fog”, cognitive disorders, dizziness, sleep disorders, depression, anxiety, posttraumatic stress disorder [PTSD]). On 6 October 2020, the World Health Organization (WHO) defined the post-COVID-19 condition as a syndrome that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset of COVID-19 with symptoms that last for at least two months and cannot be explained by an alternative diagnosis [5].

Data suggest a high risk of psychiatric and neuropsychiatric issues at the acute phase of COVID-19 in comparison with other health events as well as psychiatric sequelae afterward, suggesting a role for specific mechanisms [6]. The post-COVID-19 condition, in particular psychiatric and neuropsychiatric post-COVID-19 symptoms, follows mild to severe forms of the acute phase of COVID-19, but its pathophysiology remains unclear [6].

2. Frequent Psychiatric and Neuropsychiatric Symptoms of Post-COVID-19 Syndrome

Studies that focus on post-COVID-19 syndrome show a frequent and high rate of depression varying from 30 to 40% [7]. Typical symptoms of depression that confirm post-COVID-19 syndrome include depressed mood, psychomotor slowdown, suicidal ideas or suicide attempts, anhedonia, abulia, and sleep and appetite disorders. Depressive symptoms can correspond with a depressive type of adjustment disorder or major depressive episodes. Although fatigue is present in more than 10% of patients with long COVID-19 [3], it is important to differentiate it from the fatigue that characterizes depressive syndrome. Fatigue in the depressive syndrome can regress with physical activity, whereas fatigue that is observed in long COVID-19 independently of a depressive comorbidity worsens with physical activity. This characteristic is similar to what occurs in chronic fatigue syndrome and appears to be unstable. Symptoms of anxiety are also frequent and mostly correspond to the anxious type of adjustment disorder criteria, but obsessive-compulsive disorders have also been described [8][7][9][10][11]. In addition, sleep disorders have been described, reaching a prevalence of 40% [10].

In addition to these symptoms, many patients with post-COVID-19 syndrome show hyperventilation syndrome. This dysfunctional breathing pattern generates dyspnea, the prevalence of which is still unknown. Often associated with, or secondary to, anxiety or depressive disorders [12], this functional disorder can be explained by the fact that dyspnea becomes an anxiety-inducing stimulus and that stress maintains the process. Hyperventilation syndrome induces many other symptoms, some of which are related to hypocapnia. These symptoms related to hypocapnia can also be anxiety-inducing (e.g., yawning, sighing, mouth breathing, irritative cough, typical chest pain, palpitations or peripheral vasospasm with coldness, neurovegetative disorders, visual disturbances, tinnitus, tremor, myalgia or cramps, migrainelike headaches, paresthesia). Diagnosis must be made by a primary care physician and confirmed by a pulmonologist after obtaining blood gas measurements, a clinical Nijmegen score, and an induced hyperventilation test [12]. According to the good practice of functional disorders, this diagnosis must be announced and explained.

COVID-19 potentially constitutes a traumatic event because of its lethality and unpredictability, which was especially true during the first wave. Peritraumatic dissociation occurred in 44.9% of patients during hospitalization for COVID-19, and the rate of PTSD more than four weeks after the acute phase varied in studies from 10.6% to 30% [7][9][10][11]. Although the neurological etiology of cognitive disorders has to be considered, it is not the only explanation. Cognitive symptoms are common in most psychiatric disorders, and some of the cognitive disorders observed in post-COVID-19 syndrome are classic outside this context. In major depression, either unipolar or bipolar, many neurobiological mechanisms such as disruption of monoaminergic transmission, dysregulation of the hypothalamic-pituitary-adrenal axis and the stress response, neuroinflammation, deficiency of neurogenesis, and neuroplasticity are involved. These perturbations result in impaired short-term memory, giving rise to an encoding disorder in long-term memory, in particular at the level of episodic and semantic memory that involves the emotional valence of memories. Such perturbations also result in disorders in executive functions with impaired procedural memory [13][14]. In PTSD, hyperactivation and augmentation in the volume of the amygdala and nucleus accumbens, on the one hand, and hypoactivation and a decrease in the volume of the prefrontal cortex and hippocampus, on the other, are involved in many cognitive impairments that are also debilitating for patients. Short-term memory associated with the trauma is fragmented with coexisting hypermnesia and amnesia of the traumatic event [15]. Memory unrelated to the trauma is also impaired. Autobiographical memory is altered concerning positive valence memories, and spatial verbal memory is altered through the disruption of recovery mechanisms and disturbances in attention and concentration. Many disorders of executive functions are observed regarding cognitive flexibility, with perseverance, working memory, and attentional disturbances via vegetative overactivation making disengagement from aversive stimuli impossible [15]. The characterization of cognitive symptoms by a neurologist and, when necessary, a neuropsychological assessment are useful. It aids in understanding the impaired cognitive functions in order to adapt management strategies. Neuroimaging, electroencephalograms, and lumbar techniques can also help explore cognitive disorders when neurological disorders are suspected. In the context of post-COVID-19 syndrome, some typical cognitive symptoms associated with psychiatric issues can be wrongly attributed to direct and indirect neurobiological effects of SARS-CoV-2, although they are manifestations of a psychiatric disorder that needs to be treated. Some functional neurological disorders can also appear in this context and should be diagnosed after neurological investigation to exclude an organic cause.

Polyphagia was also clinically observed in post-COVID-19 syndrome in some patients [16]. The possible mechanism might be related to the CNS meningoencephalitis following SARS-CoV-2 infection and the subsequent degeneration of neuronal and glial cells due to smoldering inflammatory response to SARS-CoV-2 virions, leading to neuronal degeneration .

3. Mechanisms Involved in Psychiatric and Neuropsychiatric Post-COVID-19

Stress is likely involved in psychiatric issues associated with having COVID-19 in both the short- and the long-term [16][17]. Many studies of the general population have also shown the presence of psychiatric issues during the COVID-19 pandemic, suggesting that stress plays a part [17]. Worldwide, people had to adapt to sanitary rules, social isolation, job loss, economic issues, and multiple and traumatic bereavements, in addition to the fear of being contaminated and the risk of potential complications of COVID-19. Contamination by SARS-CoV-2 at the acute phase could have been a highly stressful—even traumatic –event because of the fear of dying or of experiencing physical sequelae. It may have induced psychiatric issues such as depression, anxiety, and PTSD. Experiencing a physical illness, especially respiratory disease, is known to be a risk factor for these psychiatric complications, and a stress mechanism such as psychiatric history, previous traumatic events, and medical prognosis [18] should be considered among other known risk factors. In patients with post-COVID-19 syndrome, the fear of reinfection, the uncertainty concerning disease evolution, and the inability to return to work create a heavy stress burden.

The other etiological possibilities of post-COVID-19 syndrome remain unclear. It could result from the viral persistence of SARS-CoV-2, an autoimmune disease, and/or persistent inflammatory factors [10][19]. Psychiatric and neuropsychiatric post-COVID-19, as is the case for the physical symptoms of long COVID-19, could be associated with these specific SARS-CoV-2 mechanisms. Persistent neuroinflammatory mechanisms, for example, have been suspected in the pathophysiology of psychiatric post-COVID-19 syndrome. These mechanisms are involved in depression because of the depletion of brain serotonin, dysregulation of the hypothalamus-pituitary-adrenal axis, and alteration of the continuous production of adult-generated neurons in the dentate gyrus of the hippocampus [19]. During the acute phase of severe forms of COVID-19, cytokine storm has been described, and persistent neuroinflammatory mechanisms could explain the post-COVID-19 condition and facilitate psychiatric issues by involving dysfunction of mitochondria and microglia [20]. A study at two to three months after COVID-19 onset showed abnormalities in cerebral magnetic resonance imaging, suggesting both an acute hypercoagulable state and chronic neuroinflammation associated with cerebrovascular diseases [10]. Inflammatory mechanisms could also be involved in psychiatric and neuropsychiatric sequelae [11], but the scant data suggest this hypothesis does not allow confirmation. The severity of depression and anxiety was not consistently associated with blood markers of inflammation [10][11], but more specific investigations on inflammatory and immunological mechanisms are needed.

At the acute phase, the SARS-CoV-2 virus uses angiotensin-converting enzyme 2 (ACE2) as a viral receptor to enter the cell by attaching its spike protein to the ACE2 receptor (ACE2-R), thereby reducing its availability. However, reduced availability of ACE-2R has an effect on the hypothalamic-pituitary-adrenal stress axis by leading to a decrease in the mechanism downstream of the corticotropin-releasing hormone in the hypothalamus. That results in decreased production of glucocorticoids [20]. Because glucocorticoids limit excessive inflammation and prevent overactivation of the stress response, decreased production creates a perpetual stress response. This feedback loop is further maintained by stressful environmental conditions and comorbid psychiatric conditions that are produced in COVID-19 disease. In addition, the ACE2-R peripherally stimulates the sympathetic pathway, thus activating the adrenals and the production of glucocorticoids. Although the role of ACE2-R has been described in psychiatric issues at the acute phase of COVID-19, its role in psychiatric sequelae remains hypothetical.

Concerning risk factors of psychiatric and neuropsychiatric sequelae after acute COVID-19, although intensive care unit (ICU) survivors are at high risk of developing psychiatric and neuropsychiatric complications such as post-intensive care syndrome (19% to 22%) [21], previous data do not show an increased risk of psychiatric and neuropsychiatric issues for COVID-19 survivors who were admitted to the ICU compared to non-ICU COVID-19 survivors. Psychiatric and neuropsychiatric issues occur after mild to severe forms of the acute phase of COVID-19 [6][9][10]. The psychiatric and neuropsychiatric risk is more frequent in women than in men [6][9]. Finally, the etiology of psychiatric and neuropsychiatric post-COVID-19 symptoms is probably multifactorial and includes an environmental stress load effect, a personal history of previous traumatic events, personal and family psychiatric antecedents, immunological and neuroinflammatory factors, and potential viral persistence, as well as genetic factors that have previously been known to be involved in psychiatric disorders.

References

1. Alwan, N.A.; Johnson, L. Defining long COVID: Going back to the start. Med 2021, 2, 501–504.
2. National Institute of Health. Available online: https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-launches-new-initiative-study-long-COVID-19 (accessed on 5 February 2022).
3. Nehme, M.; Braillard, O.; Alcoba, G.; Perone, S.A.; Courvoisier, D.; Chappuis, F.; Guessous, I. COVID-19 Symptoms: Longitudinal Evolution and Persistence in Outpatient Settings. Ann. Intern. Med. 2021, 174, 723–725.
4. Dani, M.; Dirksen, A.; Taraborrelli, P.; Torocastro, M.; Panagopoulos, D.; Sutton, R.; Lim, P.B. Autonomic dysfunction in ‘long COVID’: Rationale, physiology and management strategies. Clin. Med. 2020, 21, e63–e67.
5. World Health Organization. Available online: WHO/2019-nCoV/Post_COVID-19_condition/Clinical_case_definition/2021.1 (accessed on 5 February 2022).
6. Taquet, M.; Luciano, S.; Geddes, J.R.; Harrison, P.J. Bidirectional associations between COVID-19 and psychiatric disorder: Retrospective cohort studies of 62 354 COVID-19 cases in the USA. Lancet Psychiatry 2020, 8, 130–140.
7. Nalbandian, A.; Sehgal, K.; Gupta, A.; Madhavan, M.V.; McGroder, C.; Stevens, J.S.; Cook, J.R.; Nordvig, A.S.; Shalev, D.; Sehrawat, T.S.; et al. Post-acute COVID-19 syndrome. Nat. Med. 2021, 27, 601–615.
8. Callard, F.; Perego, E. How and why patients made Long COVID. Soc. Sci. Med. 2020, 268, 113426.

9. Benzakour, L.; Braillard, O.; Mazzola, V.; Gex, D.; Nehme, M.; Perone, S.A.; Agoritsas, T.; Kopp, G.; Cereghetti, S.; Bondolfi, G.; et al. Impact of peritraumatic dissociation in hospitalized patients with COVID-19 pneumonia: A longitudinal study. J. Psychiatr. Res. 2021, 140, 53–59.
10. Raman, B.; Cassar, M.P.; Tunnicliffe, E.M.; Filippini, N.; Griffanti, L.; Alfaro-Almagro, F.; Okell, T.; Sheerin, F.; Xie, C.; Mahmod, M.; et al. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. eClinicalMedicine 2021, 31, 100683.
11. Mazza, M.G.; De Lorenzo, R.; Conte, C.; Poletti, S.; Vai, B.; Bollettini, I.; Melloni, E.M.T.; Furlan, R.; Ciceri, F.; Rovere-Querini, P.; et al. Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. Brain Behav. Immun. 2020, 89, 594–600.
12. Taverne, J.; Salvator, H.; Leboulch, C.; Barizien, N.; Ballester, M.; Imhaus, E.; Chabi-Charvillat, M.-L.; Boulin, A.; Goyard, C.; Chabrol, A.; et al. High incidence of hyperventilation syndrome after COVID-19. J. Thorac. Dis. 2021, 13, 3918–3922.
13. Culpepper, L.; Lam, R.W.; McIntyre, R.S. Cognitive Impairment in Patients With Depression: Awareness, Assessment, and Management. J. Clin. Psychiatry 2017, 78, 1383–1394.
14. Lima, I.M.; Peckham, A.D.; Johnson, S.L. Cognitive deficits in bipolar disorders: Implications for emotion. Clin. Psychol. Rev. 2017, 59, 126–136.
15. Gindt, M.; Hot, P. Cognitive impairment in trauma. In Knowledge to Heal; Canini, F., El-Hage, W., Eds.; Mona Edition: Paris, France, 2017; pp. 201–209.
16. Kaggwa, M.M.; Favina, A.; Najjuka, S.M.; Zeba, Z.; Mamun, M.A.; Bongomin, F. Excessive eating and weight gain:A rare post-acute COVID-19 syndrome. Diabetes Metab. Syndr. Clin. Res. Rev. 2021, 15, 102252.
17. Cénat, J.M.; Blais-Rochette, C.; Kokou-Kpolou, C.K.; Noorishad, P.-G.; Mukunzi, J.N.; McIntee, S.-E.; Dalexis, R.D.; Goulet, M.-A.; Labelle, P.R. Prevalence of symptoms of depression, anxiety, insomnia, posttraumatic stress disorder, and psychological distress among populations affected by the COVID-19 pandemic: A systematic review and meta-analysis. Psychiatry Res. 2021, 295, 113599.
18. Luo, M.; Guo, L.; Yu, M.; Jiang, W.; Wang, H. The psychological and mental impact of coronavirus disease 2019 (COVID-19) on medical staff and general public—A systematic review and meta-analysis. Psychiatry Res. 2020, 291, 113190.
19. Yohannes, A.M.; Newman, M.; Kunik, M.E. Psychiatric Collaborative Care for Patients With Respiratory Disease. Chest 2019, 155, 1288–1295.
20. Troubat, R.; Barone, P.; Leman, S.; DeSmidt, T.; Cressant, A.; Atanasova, B.; Brizard, B.; El Hage, W.; Surget, A.; Belzung, C.; et al. Neuroinflammation and depression: A review. Eur. J. Neurosci. 2020, 53, 151–171.
21. van Vuren, E.J.; Steyn, S.F.; Brink, C.B.; Möller, M.; Viljoen, F.P.; Harvey, B.H. The neuropsychiatric manifestations of COVID-19: Interactions with psychiatric illness and pharmacological treatment. Biomed. Pharmacother. 2021, 135, 111200.