Post-COVID-19 Condition

Subjects: Others

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COVID-19 is currently considered a systemic infection involving multiple systems and causing chronic complications. Compared to other post-viral fatigue syndromes, these complications are wider and more intense. The most frequent symptoms are profound fatigue, dyspnea, sleep difficulties, anxiety or depression, reduced lung capacity, memory/cognitive impairment, and hyposmia/anosmia. Risk factors for this condition are severity of illness, more than five symptoms in the first week of the disease, female sex, older age, the presence of comorbidities, and a weak anti-SARS-CoV-2 antibody response. Different lines of research have attempted to explain these protracted symptoms; chronic persistent inflammation, autonomic nervous system disruption, hypometabolism, and autoimmunity may play a role. Due to thyroid high ACE expression, the key molecular complex SARS-CoV-2 uses to infect the host cells, thyroid may be a target for the coronavirus infection. Thyroid dysfunction after SARS-CoV-2 infection may be a combination of numerous mechanisms, and its role in long-COVID manifestations is not yet established. The presence of post-COVID symptoms deserves recognition of COVID-19 as a cause of post-viral fatigue syndrome. It is important to recognize the affected individuals at an early stage so researchers can offer them the most adequate treatments, helping them thrive through the uncertainty of their condition.

Keywords: post-COVID-19 condition ; long COVID ; SARS-CoV-2 ; thyroid

1. Introduction

COVID-19 was first described as a respiratory disease, but presently it is considered a systemic infection comprising multiple systems and causing chronic complications [1][2][3] (**Figure 1**). The pathology results not only from the virus infection but from an aberrant inflammatory host immune response [4]. The immune response has been well described in acute COVID-19 patients, but the lasting consequences of the infection are still not well known [4]. Researchers have been exhaustively surveying the diverse symptoms of long COVID, but until now, no integrated explanation exists for their manifestation [5]. Sykes et al. [6] alerted people to the effects of this poorly known lethal virus, to the societal disruption it has caused, and to the importance it may have in the development of long-lasting physical and mental health symptoms. On the other hand, Sancak and Kilic [1] state that post-COVID-19 condition symptoms can most often be interpreted as somatization; however, the fact that researchers may not understand them does not mean they are purely psychosomatic [1]. In the study of Xiong et al. [7] in hospitalized patients from Wuhan, a non-infected control group from the general population was used in order to exclude the psychological effects of the long and mandatory isolation period, which caused deconditioning, anxiety, and depression. The authors showed a significant difference between the group of COVID-19 “recovered” patients and the control group, with the latter reporting very few long-term symptoms [7].

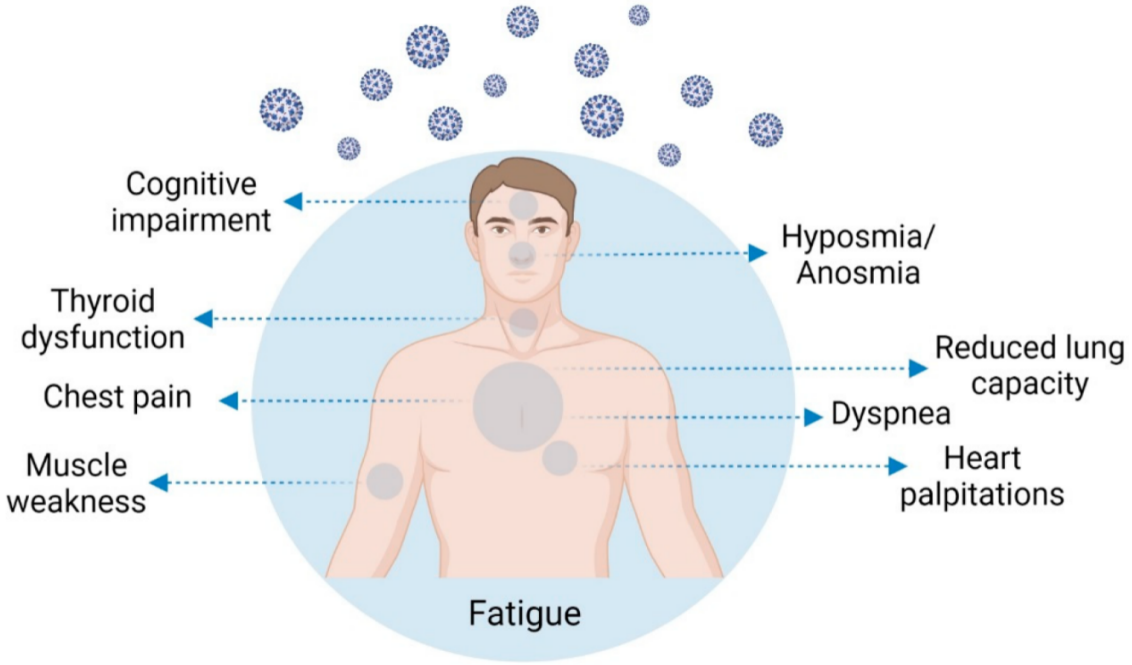

Figure 1. Examples of post-COVID-19 condition chronic complications.

2. Post-COVID-19 Condition Symptomatology and Prevalence

Protracted COVID-19 infection–related symptoms are common [8][9], but the post-COVID-19 condition [10] (previously referred to as long COVID] is a poorly understood aspect of the current pandemic [9][11]. Compared with other post-viral fatigue syndromes, the symptoms are wider and more intense [12]. An exact definition was recently published by the WHO [10]: typically, symptoms with duration ≥2 months [10][13][14] that cannot be explained by an alternative diagnosis are considered post-COVID-19 condition [10]. Post-acute manifestations may be divided into three categories: (1) residual symptoms continuing after recovery from acute infection; (2) organ dysfunction continuing after initial recovery; and (3) new symptoms or syndromes that appear after initial asymptomatic or mild infection [15].

Over several studies, the frequency of post-COVID-19 condition ranged from 4.7 to 80% (n = 25), occurring between 3 to 24 weeks after the acute phase or hospital discharge [16]. Yong [17], in a study on COVID-19 survivors (n = 10), reported that a post-COVID-19 condition persisted for one to six months in 30−80% of patients. Other studies reported a 35% prevalence of residual symptoms in non-hospitalized patients [18], but around 75–87% in hospitalized patients [6][18][19]. In a cohort of patients followed-up for three to nine months after infection, about 30% maintained persistent symptoms [20].

The most frequently reported symptoms, not restricted to severe acute disease [19][21], are profound fatigue [3][6][15][19][22][23][24][25][26][27][28][29][30] or muscle weakness [6][19][29][31], dyspnea [3][6][24][25][28][30], sleep difficulties [6][19][23][28], anxiety or depression [6][19][29], reduced lung capacity [22][32], memory/cognitive impairment (“brain fog”) [23][28][29], hyposmia/anosmia [23], and the inability to fully exercise or work. The most frequent symptom of post-COVID-19 condition is fatigue, which is independent of the acute disease severity or the presence of respiratory problems [33]. A summary of post-COVID-19 condition symptoms, with the frequencies reported and number of patients evaluated, is presented in **Table 1**. The high variability found between studies is mostly attributable to acute COVID-19 severity, with more frequent symptoms in hospitalized patients compared with patients who suffered from mild or asymptomatic disease.

Table 1. Post-COVID-19 condition symptoms most frequently reported.

Post-COVID-19 Symptoms	Number of Patients Included in the Study	% Patients Suffering from Symptom/References
Fatigue	**596, 177, 538, 270, 138, 3065, 134, 242, 115, 143, 96, 1733, 5440, 384, 287**	**13.1% [34], 13.6% [20], 28.3% [7], 34.8% [25], 39.0% [27][30], 39.6% [6], 41.7% [35], 47% [26], 53.1% [36], 56.3% [28], 63% [19], up to 65% [16], 69% [37], 72.8% [38]**
Persistent breathlessness /dyspnea	**596, 3065, 287, 270, 96, 138, 143, 384, 134, 5440, 35**	**6.0% [34], 23.2% [30], 28.2% [38], 34.0% [25], 37.5% [28], 40.0% [27], 43.4% [36], 53.0% [37], 60% [6], up to 61% [16], 80% [23]**
Myalgia /muscle weakness	**277, 242, 134, 1733**	**19.6% [25], 35,1% [35], 51.5% [6], 63% [19]**

Post-COVID-19 Symptoms	Number of Patients Included in the Study	% Patients Suffering from Symptom/References
Anxiety	287, 402, 134	38.0% [38], 42% [39], 47.8% [6]
Sleep disturbance	1733, 96, 134, 35, 138	21.1% [35], 26.0% [19], 26.0% [28], 35.1% [6], 40.0% [39], 46% [23], 49% [27]
Joint pain	277, 143, 287	19.6% [25], 27.3% [36], 31.4% [38]
Headache	242, 270, 3065, 287	19.0% [35], 19.8% [25], 23.4% [30], 28.6% [38]
Chest pain	596, 242, 538, 143, 287, 35, 5440	0.8% [34], 10.7% [35], 12.3% [7], 21.7% [36], 28.9% [38], 34.8% [23], up to 89% [16]

To better examine this issue, Gaber et al. [27] looked at the effects of COVID-19 infection in healthcare workers, a population with an expected high level of exposure to the virus. They reported a high incidence of infection and a high prevalence of incapacitating post-COVID-19 symptoms, with fatigue commonly reported [27]. Nonetheless, these health workers were unwilling to either seek medical help or take sick leave, despite their struggle to cope with the symptoms [27].

Taquet et al. [40] found a higher incidence of numerous psychiatric disorders in COVID-19 survivors compared with matched patients with influenza or other respiratory tract infections, in a retrospective cohort study using 236,379 electronic health records. The estimated incidence of a neurological or psychiatric diagnosis in the six months following a COVID-19 diagnosis was 33% (95% CI; 33.17–34.07) [40]. Post-COVID-19 condition presents neurological symptoms similar to chronic fatigue syndrome (CFS) and functional neurological disorder (FND] (except for hypogeusia) [41].

Davis et al. [42] conducted an online survey to characterize post-COVID-19 condition in an international cohort (56 countries), tracing the symptoms over 7 months. They found for 91% of the respondents that the time to recovery exceeded 35 weeks; the most frequent symptoms after six months were fatigue, post-exertional malaise, and cognitive dysfunction [42]. According to the authors, their study represents the largest collection of symptoms recognized in post-COVID-19 condition individuals to date (June 2021). More recent studies have shown that persistent symptoms can be found 12 [43] or up to 15 months after recovery from the acute phase of COVID-19 [44]; symptoms are common both in ambulatory and hospitalized patients [44].

3. Post-COVID-19 Condition Risk Factors

Post-COVID-19 condition is associated with a weak anti-SARS-CoV-2 antibody response [45], severity of illness [19][34][46][47], female sex [3][5][6][18][19][34][35][45], presence of more than five symptoms in the first week of the disease [3][18][48], older age [18], and presence of comorbidities [18]. Concretely, Fernández-de-las-Peñas et al. [49] reported that the most significant risk factor for developing more post-COVID symptoms was the number of symptoms at hospital admission, which supports the idea that a higher symptom burden in the acute phase of the disease is associated with a higher probability of the post-COVID-19 condition.

Early dyspnea, prior psychiatric disorders, and specific biomarkers (e.g., D-dimer, C- reactive protein, and lymphocyte count) have also been reported as risk factors, even though more research is needed to validate them [3]. Peghin et al. [34] suggested that the constantly elevated titers of the serological response against SARS-CoV-2 may constitute an independent risk factor for the post-COVID-19 condition, since the presence of SARS-CoV-2 IgG antibodies is significantly associated with the condition. Contrarily, Seessle et al. [28] reported that patients presenting at least one post-COVID-19 symptom 12 months after infection did not significantly differ in their SARS-CoV-2 antibody levels when compared with patients without symptoms, although their physical and mental quality of life had significantly decreased.

Interestingly, Townsend et al. [26] showed that significant illness persistence after the COVID-19 acute phase of the disease, affecting health perception, ability to return to work, and the existence of lasting fatigue, appears to be unrelated to the severity of the acute phase, though one would expect to see a difference in post-COVID symptoms between hospitalized and non-hospitalized patients; this hypothesis needs to be verified in upcoming studies [50]. In fact, one puzzling feature of post-COVID-19 condition is that it affects COVID-19 patients at all disease severity levels [3], often affecting patients with a mild acute illness [51]. Studies have shown that post-COVID-19 condition affects even mild to moderate cases [3][52][53] and younger adults (or even children) who did not need respiratory support or hospital or intensive care [3]. Post-COVID-19 condition in children is similar to that seen in adults [54], with symptoms such as a fatigue, dyspnea, myalgia, cognitive impairments, headache, palpitations and chest pain [3][55].

In general, it appears that the ratio for post-COVID-19 condition development is 2:1 in women compared with men, but only until around age 60, when the ratio between women and men becomes similar [14].

Post-COVID-19 condition in patients with comorbidities may result from their comorbidity worsening [56].

4. Post-COVID-19 Condition Pathophysiology

Different lines of research are trying to explain these protracted symptoms. A persistent immune activation and/or inflammation may contribute to post-COVID-19 condition, which could explain why many patients with mild COVID-19 disease experience chronic persistent symptoms, involving the cardiovascular, nervous, and respiratory systems [57]. In fact, the persistently elevated inflammatory markers observed in long-COVID patients point towards chronic persistence of inflammation [18][58].

Seessle et al. [28] observed several neurocognitive symptoms that were associated with antinuclear antibody titer elevation, pointing to autoimmunity as a cofactor in the etiology of post-COVID-19 neurologic conditions [28]. The autoimmune hypothesis could explain the greater incidence of this condition in women [14][57]. Since thyroid is closely linked to T-cell-mediated autoimmunity, thyroid dysfunction may be important in the pathophysiology of post-COVID-19 condition, as discussed in more detail below [3].

Post-COVID-19 condition has been related to additional characteristics of the innate and adaptive response, involving a weaker initial inflammatory response, with lower baseline levels of C-reactive protein and ferritin [45]. The participation of the immune system in post-COVID-19 condition has been reported in other studies [8][21][57][59][60]. Symptoms such as cognitive dysfunction, persistent fatigue, muscle aches, depression, and other mental health issues are highly associated with an initial immune challenge and/or with a constant dysregulation of the immune system [29][60].

The involvement of inflammatory cytokines in the etiology of the neuropsychiatric symptoms, reported in current large-scale population-based epidemiological and genetic studies, indicates that these cytokines may have a role in the etiology of the neuropsychiatric symptoms usually observed in patients with post-COVID-19 condition [3][29][60]. This cytokine storm must also be considered as a possible driving factor for the expansion of neuropathies after severe COVID-19 infection, contributing to the chronic pain that appears after acute infection recovery [61].

Studies have shown that patients with severe symptoms may have more severe autonomic dysfunction when compared with patients presenting mild symptoms, as indicated by the heart rate variability (HRV) analysis [2], which is a reliable non-invasive tool used to evaluate autonomic modulation [2][62]. Patients with severe symptoms presenting amelioration in autonomic parameters also show enhancements in immune and coagulation functions, as well as in cardiac injury biomarkers [2].

5. Thyroid Involvement in COVID-19

Due to the reported high expression of ACE2, the thyroid may become a target of coronavirus infection, and thyroid involvement in COVID-19 patients has been demonstrated [63]. In fact, SARS-CoV-2 uses ACE2, combined with the transmembrane protease serine 2 (TMPRSS2), as the main molecular complex for the host cell infection [64]. Interestingly, ACE2 and TMPRSS2 expression levels are higher in the thyroid gland than in the lungs [64]. Scappaticcio et al. [64], in their literature review on thyroid dysfunction in COVID-19 patients, presented strong evidence that the thyroid gland and the entire hypothalamic–pituitary–thyroid (HPT) axis may be important targets for SARS-CoV-2 damage.

Campi et al. [63] found a temporary situation of low TSH with normal T4 and low T3 levels in patients hospitalized for SARS-CoV-2 infection, which was inversely associated with C-reactive protein, cortisol, and IL-6, and positively associated with normal Tg levels. These authors stated that this temporary change was probably due to the cytokine storm induced by the virus, with a direct or mediated impact on TSH secretion and deiodinase activity, and probably not to a destructive thyroiditis. The THYRCOV study offers early evidence that patients with acute SARS-CoV-2 infection with thyrotoxicosis have statistically significantly higher levels of IL-6 [65]. In a short-term follow-up, Pizzocaro et al. [66] showed a spontaneous normalization of thyroid function in most infected patients with SARS-CoV-2-related thyrotoxicosis. Nevertheless, these authors stated that long-lasting studies are needed, since they found a frequent thyroid hypoecogenicity pattern in the ultrasonographic evaluation of these patients, which may predispose them to late-onset thyroid dysfunction development [66].

Even though clear evidence is missing, infection of the thyrocyte, thyrotroph, and corticotroph may lead to a decrease in T3, T4, TSH, ACTH, and cortisol levels [67]. HPT dysregulation has been considered, at least in part, responsible for hypothyroidism in COVID-19 [67][68]. Low FT3 levels are independently associated with increased mortality [67][69][70] and

disease severity [68][71][72][73] and may be used as a surrogate prognostic biomarker [67][69][70].

Researchers' knowledge of the thyroid patterns of COVID-19 is still incomplete, as is the etiologic view of COVID-19 and thyroid insults [67][74]. To find direct evidence concerning the nature and cause of thyroid SARS-CoV-2 injury, and the full immune response in those patients with thyroid dysfunction, researchers need a histologic and cytological examination of the thyroid gland in a wide number of patients [67][68].

6. Post-COVID-19 Condition Health Burden and Patient Management

Post-COVID-19 condition (or long COVID) first gained extensive credit among social support groups, and then in scientific and medical communities [3][5][75][76]. It is probably the first illness to be cooperatively identified by patients discovering one another using Twitter and other social media [75].

Patients with post-COVID-19 condition are a heterogeneous group, which makes it difficult to advise treatment [77][78]. It is crucial for each patient to find the correct equilibrium between mild activity to avoid deconditioning and not triggering post-exercise malaise [77]. Strategies tackling levels of stress and/or the stress response, comprising psychosocial intervention, physical exercise, or possibly dietary interventions of people could be a good approach to counteract some of the negative effects of chronic inflammation [29].

Management of post-acute COVID-19 syndrome requires a comprehensive team, including physicians of various specialties (primary care, pulmonology, cardiology, and infectious disease), physiatrists, behavioural health experts, physical and occupational therapists, and social workers, which will address the clinical and psychological aspects of the disease [79].

7. Conclusions

It is urgent to better understand this emerging, complex, and puzzling medical condition [16][80]. Post-COVID-19 condition can become a crisis for health systems, which are already facing the challenge of the pandemic [81]. The primary care services, which represent the first approach for patient diagnosis, still have little information or resources to deal with these patients [82].

There is an urgent need to identify affected individuals early so the most appropriate and efficient treatments may be provided [79][80], helping them to thrive through the uncertainty of their condition [15][83].

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