Post-COVID Syndrome

Subjects: Infectious Diseases
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Post-COVID syndrome is increasingly recognized as a new clinical entity in the context of SARS-CoV-2 infection.

Keywords: COVID-19 ; SARS-CoV-2 ; inflammation ; post-infectious

1. Introduction

More than a year after the declaration of the coronavirus disease 2019 (COVID-19) pandemic, the world continues to face its devastating impact, not only on morbidity, mortality, and healthcare services, but also its tremendous societal and economic consequences, globally [1]. Although the overwhelming body of knowledge on COVID-19 focuses almost exclusively on acute illness [2][3][4], it has become evident that long-term consequences occur [5][6].

Post-COVID syndrome was described for the first time in spring 2020 in the context of a survey of prolonged COVID-19 symptoms, run by the Patient-Led Research Collaborative, citizen's scientist group [7]. Soon after the first COVID-19 cases evolved, they observed that COVID-19 patients had symptoms persisting for several weeks after acute infection [7]. The most common post-COVID symptoms include fatigue, dyspnea, olfactory and gustatory dysfunction, chest pain, myalgia, and sleep and mental disorders [6][7][8][9][10]. Symptoms may last for several months and disrupt work activities and the quality of life of affected individuals [6]. In recent months, our knowledge on post-COVID syndrome has expanded, mainly due to the recognition of new clinical manifestations, including rare neurological and thromboembolic complications, while the long-term consequences of the disease remain largely unknown [7][8][9][11][12][13]. It is estimated that 10% to 35% of patients not requiring hospitalization develop post-COVID symptoms, regardless of co-morbidities [6][14][15], while incidence rates up to 80% have been reported among hospitalized patients and among patients with severe illnesses [16][17][18].

2. Definition of Post-COVID Syndrome

Currently, there is no universally accepted definition of post-COVID syndrome. Post-COVID syndrome was defined for the first time by Greenhalgh et al. as COVID-19 associated illness extending for more than three weeks after the onset of symptoms, and chronic COVID-19 as persistent symptoms extending beyond 12 weeks after the onset of symptoms [7][14]. Recently, Amenta et al. proposed to the definitions outlined by Greenhalgh et al. that for patients who remain hospitalized at three weeks after symptom onset, the post-acute period starts when the patient is discharged from inpatient acute care [19].

3. Classification of Post-COVID Syndrome

According to the proposed criteria of the University of Cincinnati Medical Center for COVID-19 sequelae, there are five categories of long COVID-19 syndrome, based on initial symptoms, time of onset, and duration of symptoms and period of quiescence (Table 1): Type 1 includes patients with a varying duration of recovery that directly relates to the severity of the acute infection, organ complications, and underlying medical conditions; Type 2 is characterized by symptoms persisting six weeks from the onset of illness; Type 3 shows a period of quiescence or nearly full recovery, followed by a recurrence of symptoms persisting for at least three months (Type 3A) or at least six months (Type 3B); Type 4 refers to patients who are initially asymptomatic at the time of a positive SARS-CoV-2 test but become symptomatic one to three months (Type 4A), or at least three months later (Type 4B); and Type 5 includes patients who are asymptomatic or have few symptoms at the time of diagnosis and die within the next 12 months [18]. Amenta et al. from Baylor College of Medicine, Houston, classified post-acute COVID-19 manifestations in three categories, of which the first two should not be regarded as mutually exclusive: (1) residual symptoms that persist after recovery from acute infection; (2) organ dysfunction that persists after initial recovery; and (3) new symptoms or syndromes that develop after initial asymptomatic or mild infection [19]. Lastly, Fernandez-de-Las Penas et al. considered also undiagnosed cases and proposed a time-based classification

as follows: potentially infection-related symptoms (up to 4–5 weeks), acute post-COVID symptoms (from week 5 to week 12), long post-COVID symptoms (from week 12 to week 24), and persistent post-COVID symptoms (lasting more than 24 weeks). Intrinsic and extrinsic predisposing factors are also considered [20]. A consensus-based standardization of definition and classification of post-COVID syndrome is needed to provide a common denominator for diagnostic and therapeutic approaches, but also for research purposes.

Table 1. Classifications of post-COVID syndrome *.

Becker et al. [18] (COVID-19 Clinic of the University of Cincinnati Medical Center)							
	Type 1	**Type 2**	**Type 3**		**Type 4**		**Type 5**
Initial symptoms	**Variable [a]**	**Mild**	**A**	**B**	**A**	**B**	**None**
			Mild	**Mild**	**None**	**None**	
Duration of symptoms	**Variable [a]**	**>6 weeks**	**3–6 months**	**>6 months**	**Variable**	**Variable**	**N/A**
Period of quiescence	**No**	**No**	**Yes**	**Yes**	**No**	**No**	**N/A**
Delayed onset of symptoms	**No**	**No**	**No**		**Yes ≥3 months**	**Yes ≥6 months**	**Yes**
Amenta et al. [19] (Department of Medicine, Baylor College of Medicine, Houston)							
MIS: >3 weeks from suspected infection							
Persisting symptoms: >3 weeks from symptom onset							
Organ dysfunction: Time of hospital discharge (if >3 weeks after symptom onset)							
Fernández-de-las-Peñas et al. [20] (Department of Physical Therapy, Occupational Therapy, Physical Medicine and Rehabilitation, Universidad Rey Juan Carlos)							
Transition Phase:Symptoms potentially associated with acute COVID-19: symptoms up to 4–5 weeks							
Phase 1:Acute post-COVID symptoms: symptoms from week 5 to week 12							
Phase 2:Long post-COVID symptoms: symptoms from week 12 to week 24							
Phase 3:Persistent post-COVID symptoms: symptoms lasting more than 24 weeks							

[a] Correlate with the severity of the initial infection, number of organ system injured and pre-existing medical conditions * as of 30 March 2020.

4. Pathogenesis of Post-COVID Syndrome

COVID-19 is a multi-system infection [21]. The cell surface angiotensin-converting enzyme 2 (ACE2) receptor, which is abundant in cells of most organs, is the main target for SARS-CoV-2 binding and infection [22][23]. A monocyte-macrophage, CD4 and CD8 cellular response, and a controlled inflammatory response occur, which results in an uncomplicated recovery of most patients [21]. A SARS-CoV-2 immune dysregulation, associated with elevated levels of cytokines interleukin-1β (IL-1β), IL-6, IL-2, and IL-10 (“cytokine storm”) and profound inflammation, is found in patients with severe life-threatening illnesses [21].

The pathogenesis of post-COVID syndrome remains largely unknown. Evidence suggests that prolonged inflammation has a key role in the pathogenesis of most post-COVID manifestations. Ortelli et al. recently studied 12 patients (median age: 67 years), who had recovered from COVID-19 with neurological complications and who complained of fatigue (median time from onset of COVID-19: 12 weeks; range: 9–13 weeks) [23]. All 12 patients had a hyper-inflammatory acute phase (markedly elevated C-reactive protein CRP and IL-6) [24]. The authors used neuropsychological and neurophysiological investigations, in comparison to 12 matched by age and gender healthy subjects, and found evidence for central abnormal neuromuscular fatigue, impaired cognitive control, reduced global cognition, apathy, and executive dysfunction in the post-COVID period, affecting their daily life [24]. Alteration of neuronal function in the context of the profound increase of circulating cytokines, and particularly IL-6, which can penetrate the blood-brain barrier, may occur and contribute to central nervous system (CNS) complications (e.g., altered mental status and neurocognitive disorders among others) [22]. In addition, COVID-19-associated inflammation might lead to Gamma–aminobutyric acid (GABA)-ergic

impairment, possibly representing the basis of neuromotor and cognitive fatigue, and explaining apathy and executive deficits [25]. Indeed, animal models have shown that an IL-6 hyper-inflammatory-induced state may decrease the density of GABA receptors [25].

In another study conducted to elucidate the underlying mechanism of neurological complaints and cognitive dysfunction in post-COVID syndrome, plasma from 24 individuals (mean age: 45.3 years) recovering from COVID-19 was tested for cytokines, antibody titers and neuronal-enriched extra-cellular (nEV) protein cargo vehicles, at a median of 60 days (range: 30–103 days) from onset of symptoms [11]. They found that the cargo of the nEVs from all recovering COVID-19 patients, regardless of time after infection, was altered. However, it was unknown if these neurodegenerative proteins are transient or long-term; if this is the case, it may indicate continuing neuroinflammation or a signal to neurodegeneration [11]. In particular, a comparison of eight patients with neurological problems (mainly memory or cognition problems) to 16 patients with no neurological problems showed a positive association between post-COVID neurological manifestations and increased SARS-CoV-2 IgG antibody titers, increased IL-6 levels and co-morbidities [11]. Plasma IL-4 levels continued to be elevated in all 24 COVID-19 patients. IL-4 is involved in brain function, such as memory. Its elevation signals an ongoing neuroinflammation after COVID-19 infection that may influence neurological sequelae by altering nEV proteins. It is possible that patients recovering from COVID-19 may have occult neurological injury, while those with perceived neurologic symptoms may have more severe infection, as also indicated by the elevated SARS-CoV-2 antibody titers [11]. They also studied 12 pre-COVID-19 historical controls (mean age: 52.3 years) [11]. Protein markers of neuronal dysfunction including amyloid-beta, neurofilament light chain, neurogranin, total tau, and pT181-tau were all significantly increased in the nEVs of all participants recovering from COVID compared to pro-COVID-19 historical controls. A limitation of this study was the fact that neurological complaints were self-reported, with no neuropsychological testing conducted [11]. Larger studies are needed to assess if these findings are persistent and to find if patients without neurological complains are truly not affected long-term.

It is known that coronaviruses are neurotropic and may invade the blood-brain barrier and access the CNS through periphery or olfactory neurons. The hippocampus appears to be particularly vulnerable to infection, which may also contribute to post-infection memory deficit [26]. Wostyn proposed the hypothesis that post-COVID fatigue syndrome may result from damage to olfactory sensory neurons, causing a reduced outflow of cerebrospinal fluid (CSF) through the cribriform plate, and leading to congestion of the lymphatic system with subsequent toxic build-up within the CNS [27]. In addition, direct SARS-CoV-2 neuroinvasion has been proposed as a mechanism that may lead to persistent neurophychiatric complications [19], but it appears less likely on the basis of time that elapsed from initial infection.

Beyond inflammation, post-COVID fatigue may be attributed to lung dysfunction. A prospective observational three-month follow-up study of 76 patients (mean age: 41.3 years) found that serum troponin-I levels during the acute illness were significantly associated with the onset of fatigue after discharge (p-value = 0.008), while lymphopenia was significantly associated with chest tightness and palpitations on exertion after discharge (p-value = 0.004) [28]. In this series, the mean values of forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), FeV1/FVC, total lung capacity and diffusion capacity were all normal, however 42% of patients had mild pulmonary function abnormalities at three months after discharge [28]. A limitation of this study is that most patients (91%) had mild COVID-19 and no past medical history of lung function was available [28].

In a series of female patients, aged 26–50 years with symptoms compatible with post-COVID syndrome (of whom one had laboratory-confirmed COVID-19), all had orthostatic intolerance [29]. Cytokine storm is accompanied by the activation of the sympathetic system and a surge of catecholamines, which in turn trigger the production of IL-6 and other cytokines, and therefore increases inflammation injury [30]. An inflammatory-mediated impairment of the autonomous nervous system, resulting in orthostatic intolerance, has been proposed [29]. In a report of two cases of post-COVID depression, the authors showed an association between depression and interleukins, such as IL-6, which was independent of other causes of depression that occurred during the COVID-19 pandemic (e.g., due to isolation) [9]. Based on this finding, the authors suggested that the administration of specific medication to reduce the cytokine activity is justified, since the normalization of pro-inflammatory cytokines decreased depression, regardless of the use of anti-depressant treatment [9]. In a 69-year-old patient with focal refractory status epilepticus (RSE) six weeks after initial infection and recovery from severe COVID-19, the only notable laboratory findings at the time of the onset of focal RSE were the elevated serum inflammatory markers and CSF protein, IgG, and IgG index, reflecting breakdown of the blood-brain barrier and inflammation in the CNS [31]. The patient's RSE was attributed to post-infectious inflammatory response, as indicated by the raised inflammatory markers [31]. Similarly, profound inflammation, as indicated by increased levels of the cytokines tumor necrosis factor (TNF)-α, IL-1, and IL-6, leading to cochlea cell stress, has been implicated in the sudden irreversible sensorineural hearing loss that occurred in a patient with severe complicated COVID-19 [11]. Direct virus invasion in the cochlea may also account for the hearing loss [11]. Vascular impairment, in association with vascular endothelial growth

factor, IL-6 and TNFα, is also prominent in the inflammatory phase of acute respiratory distress syndrome (ARDS) and may account for post-COVID-19 pulmonary fibrosis, which is characterized by uncontrolled fibroproliferation in the context of dysregulated release of matrix metalloproteinases, leading to injury of endothelium and epithelium [32]. Likewise, infected monocytes and macrophages, which are part of the first cellular immune response to acute SARS-CoV-2 infection, may contribute to cytokine storm and massively migrate from lungs to tissues, and appear to contribute to post-COVID complications, including fibrosis, while their manipulation may open novel therapeutic perspectives [21][23][33]. High-resolution chest computed tomography has shown architectural distortion, interlobal septal thickening and traction bronchiectasis, compatible with fibrotic lung disease, in patients who continue to have hypoxia, even after three weeks of treatment, despite the improvement of their symptoms [32]. Likewise, a French prospective follow-up study of 478 hospitalized COVID-19 patients (mean age: 61 years), evaluated four months after discharge, found that 244 (51%) had at least one symptom that did not exist before COVID-19, mainly fatigue (31%), cognitive symptoms (21%), and new-onset dyspnea [4]. Lung computed tomography in 177 patients, including 97 former ICU patients, revealed abnormalities in 108 (63%) patients (mainly subtle ground-glass opacities) and fibrotic lesions in 33 (19%) patients, mainly among patients with ARDS [8]. In echocardiography, the left ventricular ejection fraction was < 50% in 8 (10%) of 83 ICU patients [8]. The authors recognize the absence of pre-COVID assessment in their cohort [8]. An Italian study of 238 patients (median age: 61 years; 59.7% men; mean of two co-morbidities) hospitalized for severe COVID-19, found that 128 (53.8%) of them had prolonged pulmonary impairment at four months post-discharge, as indicated by pulmonary function tests and diffusion lung capacity for carbon monoxide (D_{LCO}), which in turn may account for several post-COVID symptoms [34].

Post-viral infection destruction of β-pancreatic cells can occur and trigger the onset of diabetes mellitus. It has been shown that SARS-CoV-2 can infect and replicate in human pancreatic islets, in association with reduced insulin-secreting granules in pancreatic β-cells and impaired glucose-stimulated insulin secretion [35], which may explain the deterioration of glycemic control observed in diabetic patients with COVID-19 necessitating exceptionally high doses of insulin [36], but also increase the risk for onset of diabetes after COVID-19 [37]. Potential pathways of injury of pancreatic β-cells include a profound proinflammatory cytokine response, leading to a chronic low-grade inflammationactivation of the renin-angiotensin-aldosterone system, through the SARS-CoV-2 target ACE2 receptor, which is abundant in pancreatic β-cells, and enhances autoimmunity in genetically predisposed individuals [37].

Lastly, a new multisystem inflammatory syndrome in children (MIS-C), in association with SARS-CoV-2 infection, has been reported [38]. The main findings in this rare, but severe, clinical syndrome include shock, cardiac dysfunction, gastrointestinal symptoms, dermatologic/mucocutaneous symptoms, and elevated inflammatory markers (CRP, IL-6, and fibrinogen levels) [38]. There is also evidence that adult patients of all ages may develop a MIS-C-like syndrome associated with SARS-CoV-2 infection [38]. In particular, several cases have been described in adults and the term multisystem inflammatory syndrome in adults (MIS-A) has been proposed [39]. The MIS-A syndrome is characterized by a wide spectrum of cardiovascular, gastrointestinal, dermatologic, and neurologic symptoms and a temporal association with SARS-CoV-2 infection, diagnosed either through RT-PCR or serologically, indicating recent infection [39]. In contrast to severe COVID-19, a distinct characteristic of this hyperinflammatory syndrome is the absence of severe respiratory illness [39]. Similar to MIS-C in children [38], a post-infectious inflammatory pathogenetic mechanism is indicated by the fact that in one third of cases, the diagnosis of SARS-CoV-2 infection is established through serology in the absence of a positive PCR test [39]. Persistent extra-pulmonary infection is also possible, since the virus has been detected in multiple organs, including the heart, liver, brain, kidneys, and gastrointestinal tract [39]. Additional proposed mechanisms for extrapulmonary dysfunction in COVID-19 include endothelial damage and thromboinflammation, dysregulated immune responses, and dysregulation of the renin-angiotensin-aldosterone system [39]. The interval between infection and development of MIS-A is unclear, adding to the uncertainty regarding whether MIS-A represents a manifestation of acute infection or an entirely post-acute phenomenon. In patients who reported typical COVID-19 symptoms before MIS-A onset, MIS-A was experienced approximately 2–5 weeks later [39]. However, eight MIS-A patients reported no preceding respiratory symptoms, making it difficult to estimate when initial infection occurred [39]. Given the high proportion of MIS-A patients with negative PCR testing, clinical guidelines recommend the use of both antibody and viral testing to assist with diagnosis [39]. In patients with atypical or late manifestations of SARS-CoV-2 infection, including MIS-A, positive antibody results might be crucial to augment clinical recognition of this condition and guide treatment [39]. In addition, the use of a panel of laboratory tests for inflammation, hypercoagulability, and organ damage (e.g., CRP, ferritin, D-dimer, cardiac enzymes, liver enzymes, and creatinine) might assist in the early identification and management of this COVID-19–associated condition [39]. Further research is needed to understand the pathogenesis and long-term effects of this newly described condition.

Endothelial cell infection through viremia is also a major pathogenic mechanism in acute COVID-19, contributing to thrombosis and bleeding (e.g., pulmonary emboli) [23]. Vascular dysfunction also appears to be implicated in post-COVID syndrome. Four weeks after PCR diagnosis of COVID-19, a 64-year-old woman developed cerebral hypoperfusion

syndrome, along with both central (dizziness, brain fog) and peripheral (distal burning sensation) nervous system dysfunction, which are indicative of reduced orthostatic cerebral blood flow [40]. In this case, abnormal arterial vasoconstriction and immune-mediated dysfunction most probably caused cerebral autoregulatory failure; IVIG administration resulted in the subsidence of symptoms, which is consistent with an autoimmune mechanism, triggered by COVID-19 [40]. In addition, in a previously healthy 56-year-old man with persistent neurological disorders, including short-duration epileptic seizures, and deep depression almost six months after COVID-19, CNS MRI revealed numerous hyperintense focal areas in the periventricular and subcortical white matter and in semioval centers, compatible with gliotic outcomes in association with microvascular injuries [41]. Endothelial injury, either due to virus invasion or in the context of profound inflammation increased levels of coagulation factors, hypoxia, due to respiratory impairment or anti-platelel factor 4 (PF4)-immune complexes, has been implicated in acute COVID-19 pathogenesis, predisposing to coagulopathy and thromboembolic complications in large blood vessels and microcirculation [21][42][43]. Thromboembolism may also complicate the post-COVID period in the context of a hypercoagulate state [44]. An increased risk of developing pulmonary thromboembolism, deep vein thrombosis, and thrombosis in other systems manifested by active bleed, has been recorded in patients who have recovered from COVID-19 [44]. Follow-up of at least 30 days post-discharge is required, while patients at high-risk for thrombosis should receive anticoagulation medications for a prolonged period [44]. A recent study from Ireland found increased D-dimer levels (>500 ng/mL) in 25.3% of 150 COVID-19 patients, including 60 with a history of hospitalization, up to four months after initial diagnosis [45]. In this latter study, increased convalescent D-dimers were more common in COVID-19 patients who had required hospitalization, and in patients older than 50 years [45].

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