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EDITORIAL

Long COVID: An Emerging Puzzle

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Abstract

Some patients, estimated at ~10%, recovering from COVID-19 infection may have persistent (>4-12 weeks) symptoms and/or prolonged organ dysfunction attributed to COVID-19 infection (*long Covid*). The facets of this long Covid syndrome are slowly emerging and the chronic impact of this viral pandemic is gradually unfolding. All these issues are herein reviewed. ***Rhythmos 2021;16(1): 1-6***.

Key Words: COVID-19; SARS-CoV-2; long Covid; post-viral fatigue syndrome; post-ICU syndrome; multisystem inflammatory syndrome; late sequelae; digital health

Abbreviations: AF = atrial fibrillation; ARDS = acute respiratory distress syndrome; COVID-19 = corona virus disease 2019; CT = computed tomography; ICU = intensive care unit; LVEF = left ventricular ejection fraction; MCAS = mast cell activation syndrome; MIS = multisystem inflammatory syndrome; PCNS = post Covid-19 neurological syndrome; PICS = post-intensive care syndrome; PTSD = post-traumatic stress disorder

Introduction

The current pandemic of COVID-19 infection with its acute effects has ushered in an era of global health and economic turmoil.[1-5] However, several reports indicate that lingering (≥4 weeks) health issues are present in a considerable proportion of patients who have recovered from COVID-19 infection pointing to a "Long COVID-19" or "Long-Haul COVID" or "Long-Tail COVID", or post COVID-19 (post-viral) syndrome or chronic COVID syndrome, even in mild disease and/or non-hospitalized patients.[6-8] It is estimated that 1 in 5 individuals have symptoms that persist after 5 weeks, and 1 in 10 have symptoms for ≥12 weeks after acute COVID-19 infection.[9] Among these persistent or relapsing and remitting symptoms of long COVID, fatiguability, shortness of breath, chronic cough, sore throat, myalgias, arthralgias, atypical chest discomfort, palpitations, headaches, anxiety, depression, skin rash, diarrhea, and cognitive problems (brain fog) are the most commonly reported symptoms (**Table 1**) (www.nice.org.uk/guidance/ng188/).[10] Investigators point to at least 4 distinct clinical groups of long COVID, post-intensive care unit (ICU) syndrome (PICS), post-viral fatigue syndrome, permanent organ damage, and long-term COVID-19 syndrome.[11] Others indicate that drug-induced adverse effects, complications of COVID-19

infection (e.g., pneumothorax, pulmonary thrombosis/ thromboembolism, myocardial infarction, stroke, etc.), post-COVID-19 neuropsychiatric problems and other infections or superinfections (bacterial, other viral, fungal) or re-infection with SARS-CoV-2 itself can also produce similar symptoms in patients who have recovered from COVID-19 infection. [12]

A lingering malaise or fatigue similar to chronic fatigue syndrome is the most commonly reported symptom of long COVID, especially from patients cared in the ICU.[13, 14]

Long Covid Studies

According to a recent cross-sectional study comprising 384 patients (mean age 59.9 years; 62% male) followed up for a median of 54 days post discharge, 69% complained of fatigue, 53% reported persistent dyspnea, 34% cough, while 14.6% had depression.[15] In those discharged with elevated biomarkers, 30% had persistently elevated d-dimer and 9.5% had elevated C-reactive protein, while 38% of chest radiographs remained abnormal with 9% deteriorating.

Table 1. **Long Covid Symptomatology**

Fatiguability
Myalgias/arthralgias
Shortness of breath
Chest discomfort / Palpitations
Clouding of mentation
Sleep disturbances
Anxiety / Depression
Skin rash
Dizziness
Earache / Tinnitus
Anorexia
Anosmia/ageusia
Autonomic symptoms (gastroparesis, diarrhea/ constipation, night sweats, postural tachycardia/orthostatic intolerance syndromes, temperature dysregulation)

Another study assessing long COVID among 180 COVID-19 patients reported that 53% of patients complained of at least one persisting symptom after a mean of 125 days after symptoms onset, 33.3% complained of one or two symptoms and 19.4% three or more symptoms.[6] At the last follow-up, 46.7% were asymptomatic compared with 4.4 % during the acute phase. The most prevalent persistent symptoms were fatigue, loss of smell and taste, and arthralgias.

A study of 201 patients (aged 44±11 years, 70% female, 87% white, 31% healthcare workers) assessed at a median of 140 days after initial symptoms following SARS-CoV-2 infection showed a low prevalence of pre-existing conditions (obesity: 20%; hypertension: 6%; diabetes: 2%; heart disease: 4%); only 18% of individuals had been hospitalized with COVID-19.[16] Fatigue (98%), myalgias (88%), shortness of breath (87%), and headaches (83%) were the most frequently reported symptoms. Ongoing cardiorespiratory (92%) and gastrointestinal (73%) symptoms were common, and 42% of individuals had $\geq$10 symptoms. There was evidence of mild organ impairment in heart (32%), lungs (33%), kidneys (12%), liver (10%), pancreas (17%), and spleen (6%). Single (66%) and multi-organ (25%) impairment was observed, and was significantly associated with risk of prior COVID-19 hospitalization ($p<0.05$). The authors concluded that in a young, low-risk population with ongoing symptoms, ~70% of individuals had impairment in one or more organs 4 months after initial symptoms of SARS-CoV-2 infection.

A large cohort study describing the long-term health consequences of 1733 patients with COVID-19 discharged from hospital indicated that at 6 months after acute infection, patients were mainly troubled with fatigue or muscle weakness (63%), sleep difficulties (26%), and anxiety or depression (23%).[17] A considerable proportion (22–56% across different severity scales) of patients, particularly those who were more severely ill during their hospital stay, had more severe impaired pulmonary diffusion capacities and abnormal chest imaging, still detectable at 6 months after symptom onset.

Thus, a *post-COVID syndrome* with residual symptoms lasting for several months in patients who have recovered from acute COVID-19 infection has been increasingly reported.[18] It is no curious, as known from prior experience in critically ill patients, especially those who have suffered from acute respiratory distress syndrome (ARDS) and cared for in an intensive care unit (ICU), that these patients often still sustain functional limitations, and in some cases, certain symptoms may linger even over many years, and such patients seem to sustain long-term disorders, also known as post-intensive care syndrome (PICS). In most cases of long COVID, a post-infection fatigue syndrome currently dominates. However, the list of symptoms keeps getting longer (**Tables 1 & 2**). Those experiencing ongoing COVID-19 have respiratory problems, but also cardiovascular, neuropsychiatric, gastrointestinal, renal and dermatological symptoms.

Respiratory System

An observational study of 145 COVID-19 patients (aged 50-70 years) evaluated the cardiopulmonary damage at 60 and 100 days after confirmed diagnosis.[19] A total of

41% of all subjects exhibited persistent symptoms 100 days after COVID-19 onset, with *dyspnea* being most frequent (36%); other symptoms included night sweat (24%), sleep disorders (22%), or hyposmia/anosmia (19%); but with decreasing frequency compared to the acute phase of COVID-19 and the first follow-up visit at 60 days. Patients still displayed impaired lung function, with a reduced diffusing capacity in 21% of the cohort being the most prominent finding. Cardiac impairment, including a reduced left ventricular (LV) function or signs of pulmonary hypertension, was only present in a minority of patients. Computed tomography (CT) scans unveiled persisting lung pathologies in 63% of patients, mainly consisting of bilateral ground-glass opacities and/or reticulation in the lower lung lobes, without radiological signs of pulmonary fibrosis. Sequential follow-up evaluations at 60 and 100 days after COVID-19 onset demonstrated a vast improvement of both, symptoms and CT abnormalities over time. As, mentioned, a large cohort study (N=1733) showed that a considerable proportion (22–56%) of patients, particularly among the more severely ill during their hospital stay, had impaired pulmonary diffusion capacities and abnormal chest imaging manifestations, still detectable at 6 months after symptom onset.[17]

Table 2: Long Covid Conditions Experienced by UK Doctors [9]

- Myocarditis or pericarditis
- Microvascular angina
- Arrhythmias, including atrial flutter and AF
- Dysautonomia (postural orthostatic tachycardia syndrome)
- Mast cell activation syndrome
- Interstitial lung disease
- Thromboembolic disease (pulmonary emboli or cerebral venous thrombosis)
- Myelopathy, neuropathy, and neurocognitive disorders
- Renal impairment
- New-onset diabetes
- Thyroiditis
- Hepatitis and abnormal liver function tests
- New-onset allergies and anaphylaxis
- Dysphonia

Cardiovascular System

As mentioned, a study followed up 145 COVID-19 patients at 60 days (follow-up visit 1) and 100 days (visit 2).[19] Trans-thoracic echocardiography revealed a high rate of diastolic dysfunction (60% and 55% of all patients, respectively); in a smaller proportion of the cohort, signs of pulmonary hypertension or pericardial effusion were detected. Only 4 patients presented with a reduced LV ejection fraction (LVEF). The frequency of diastolic dysfunction, signs of pulmonary hypertension, and LVEF impairment did not significantly change from follow-up visit 1 to 2, however, the number of patients with pericardial effusion decreased over time (p=0.039).

Orthostatic intolerance or autonomic syndromes have also been reported as part of long COVID in survivors of SARS-CoV-2 infection, possibly as a result from deconditioning, hypovolemia or immune- or virus-mediated neuropathy.[8, 20]

Other Systems

According to a study of 125 patients reporting anosmia and ageusia during the acute phase of COVID-19 infection, 30 patients (24%) reported persistent taste and smell disorders at 6 months later. [21]

Following direct neuro-invasion of the virus, a *post Covid-19 neurological syndrome (PCNS)* has also been described.[22] The emergence of longer-term post-Covid neurological effects is increasingly reported.[23, 24] Symptoms related to this syndrome include varying degrees of depression, anxiety, cognitive decline, post-traumatic stress disorder (PTSD) and insomnia.[25, 26] Recently, a case was described of delayed onset, acute demyelinating neuropathy (Guillen-Barre syndrome), considered as part of long Covid syndrome, in a 46-year-old man who presented with bilateral leg pain and loss of sensation in his feet 53 days after having COVID-19 pneumonitis.[27] Even asymptomatic or very mildly symptomatic patients may report prolonged symptoms such as fatigue, myalgias, dizziness, headaches, and anosmia, with fatigue reported as the most prevalent symptom, being experienced for months after Covid-19 infection, highlighting the need for on-going vigilance for PCNS. [28]

Children

Children, more commonly girls, may experience similar long COVID symptoms to adults. In a case series of 5 children with potential long COVID (median age 12 years, range 9-15 years, 4 girls), symptoms persisted for 6-8 months after clinical diagnosis of COVID-19.[29] None were hospitalized at diagnosis, but one was later admitted for peri-myocarditis. All 5 children had fatigue, dyspnea, palpitations or chest pain, and 4 had headaches, difficulties concentrating, muscle weakness, dizziness and sore throats. Some had improved after 6-8 months, but they all suffered from fatigue and none had fully returned to school. In children, a post-infectious multisystem inflammatory syndrome has also been described (see discussion below).[30]

Multisystem Inflammatory Syndrome (MIS)

A particular aspect of SARS-CoV-2 infection that has been reported is the Kawasaki-like multisystem inflammatory syndrome (MIS). Initially described in children and adolescents (MIS-C),[30] MIS is thought to occur many weeks after initial mild or asymptomatic SARS-CoV-2 infection. Thus, MIS may occur in the post-infectious or post-acute period.[31] The definition for MIS-C as provided by the US Centers of Disease Control and Prevention (CDC) has several components: (1) age <21 years with fever, laboratory findings of inflammation, and severe illness affecting multiple organ systems; (2) no alternative plausible diagnosis; and (3) evidence of SARS-CoV-2 infection as demonstrated by molecular, serological, or antigen testing (or exposure to a suspected or confirmed COVID-19 case within the 4 weeks before presentation).[32] As of July 29, 2020, a total of 570 U.S. MIS-C patients who met the case definition had been reported to CDC.[33] Accumulated data suggest that MIS-C is an inflammatory condition with overlap with Kawasaki disease that most often occurs in the postinfectious period.

Recently, a detailed report from the CDC described MIS occurring in 16 adult patients (MIS-A) as opposed to children and adolescents.[34] In the 11 patients in whom SARS-CoV-2 antibodies were checked, all 11 had positive serology. Also, 6 of 16 patients had negative PCR test results. All 16 had evidence of cardiovascular effects, including arrhythmias, elevated troponin levels, or echocardiographic evidence of left or right ventricular dysfunction; 13 patients had gastrointestinal symptoms and 5 had dermatologic manifestations on admission. Despite minimal respiratory symptoms, 10 patients had pulmonary ground glass opacities, and 6 had pleural effusions identified on chest imaging. These findings suggest that MIS-A is also a post-acute or postinfectious condition.

Interestingly, it has also been suggested that the symptoms characterizing MIS are very similar to those associated with the mast cell activation syndrome (MCAS), presenting as a chronic multisystem polymorbidity of general mast cell-mediator-driven processes of inflammation and/or allergic-type conditions.[35, 36]

Multiorgan Involvement

A prospective, longitudinal, observational study (Coverscan study) in 201 patients has suggested that up to two thirds of people with long COVID have organ damage and 25% have damage to multiple organs, including the heart in 32% of patients (myocarditis in 11%; systolic dysfunction in 23%), lungs in 33%, kidneys in 12%, liver in 10%, pancreas in 17%, while 6% had evidence of splenomegaly.[16] Organ impairment was more common in hospitalized versus non-hospitalized patients.

Potential Mechanisms of Long Covid

As deduced from the wide spectrum of clinical presentations of COVID-19 infection, the etiology of long Covid symptoms may likely be multifactorial.[37] The invasion of SARS-CoV-2 of the nervous system may account for the persistent neuropsychiatric sequelae.[38] Other proposed mechanisms for persistent post-viral sequelae, e.g. the chronic fatigue syndrome, may include the virus-induced "cytokine storm" and dysregulated immune response.[39] The persistence of symptoms for a period of longer than 3 weeks, when the virus is rarely recovered beyond this time period, likely suggests that persistent symptoms are mainly driven by immunological processes. However, lingering presence of the virus in immunologically active sites within the body, where it can be difficult for the immune system to clear the virus, cannot be excluded. On the other hand, endothelial injury and ongoing endothelial dysfunction and pyroptosis (inflammatory form of programmed cell death) might also play a role in postacute symptomatology and organ dysfunction.[5] Post-ICU syndrome (PICS) may also be responsible for several long Covid symptoms, including persistent cognitive impairment, weakness, fatigue, dyspnea, and stress after hospital discharge, in those attended for in the ICU setting.[40, 41] Finally, the novel suggestion of SARS-CoV-2-induced symptomatic flaring of escalated MCAS (e.g. fatigue, myalgias) may offer another pathogenetic explanation for long Covid in some patients (see discussion above).[35]

Assessment and Management

According to the experience of patients afflicted by long Covid symptoms, there is much frustration and discontent with access to medical services regarding their confusing illness and the medical attention and care they receive.[42] The British National Institute for Health and Care Excellence (NICE) has issued guidance (www.nice.org.uk/guidance/ng188/chapter/4-Planning-care) on long Covid that recommends screening blood tests, such as full blood count; clotting profile; renal, liver, and thyroid functions; C reactive protein; and tests of both cardiac and lung function to capture reversible abnormalities. However, there is need also to screen for, diagnose, and manage medical complications reported in patients with long Covid including silent desaturations; cardiac, respiratory, renal, hepatic, gastrointestinal, and neurological abnormalities; endocrine problems;

autonomic dysregulation and postural tachycardia; and mast cell disorder.[43]

Planning rehabilitation services is recommended to manage these symptoms appropriately and maximize the functional return of COVID-19 survivors.[13] Post-ICU and posthospital discharge care that rests with clinicians other than the intensivist who provided the initial critical care, may help the recuperation of patients with PICS.[41]

Interventions that have been suggested to counter long Covid may comprise rehabilitation interventions such as progressive exercise and occupational rehabilitation, breathing techniques, psychological interventions (such as cognitive behavior therapy), and cognitive training (such as memory training).[43] On the other hand, a personalized approach may be safer, such as in cases of suspected peri-myocarditis where exercise may pose a serious risk.

Conclusion

Some patients, estimated at ~10%, recovering from COVID-19 infection may have persistent (>4-12 weeks) symptoms and/or prolonged organ dysfunction attributed to COVID-19 infection (*long Covid*), not explained by an alternative diagnosis; the term "*post-covid syndrome*" or "*chronic post-Covid syndrome*" may be used for symptoms lasting >12 weeks after infection. These long Covid syndromes are multisystem syndromes and need a multifaceted strategy and approach to tackle the physical, cognitive, neuropsychological, social, and vocational aspects of this pandemic.[9, 44] These patients ("long haulers") should be followed-up clinically and with serial measures of lung function, echocardiography, and CT scans of the chest. Health systems need to invest in multidisciplinary rehabilitation services now than later in order to reverse these lingering symptoms before they become chronic. Such an approach can prevent a future spate of chronic disability that may drain healthcare resources and impose a heavy toll on global economies. Although significant advances have been made in treating the acute phase of SARS-CoV-2 infection, very little is known about the chronic impact of this viral pandemic, which is gradually unfolding.

There is dire need for further research into the natural history of long COVID. As Covid-19 seems to settle among us for years to come, there is also need to address the complexities of the disease course, including development of new symptoms and severe abnormalities months or years after the acute phase of COVID-19 infection.[44, 45] Digital monitoring with use of mobile devices might prove very useful and helpful in tagging these patients and tackling this emerging puzzle. [3, 46] In the end, all our expectations focus on effective vaccines against COVID-19 to hopefully resolve this pandemic. [47]

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