

The prolonged effects of COVID-19. A new “threat”?

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Abstract. – Coronavirus ‘long-haulers’ currently represent a significant public health concern. Recent reports suggest that persistent effects of COVID-19, such as fatigue, dyspnea, chest pain, anxiety, depression, arthralgia, may last for months and lead to a decline in quality of life. Risk factors for long COVID are still not very well understood. Survivors suffer from ongoing symptoms. This new entity highlights the need for a multidisciplinary approach that would enable close monitoring of affected patients and implementation of measures that could reduce the impact of the pandemic on the overall patient wellbeing after the resolution of acute symptoms.

Key Words:

Long COVID, Anxiety, Risk factors, Clinical manifestations, Image findings.

Introduction

Coronavirus disease infection 2019 (COVID-19) has become a global pandemic. The clinical manifestations of COVID-19 are multiple, ranging from asymptomatic to severe respiratory infection, Acute Respiratory Distress Syndrome (ARDS), and death. The disease course seems milder in children, yet a small proportion develops severe disease that may in some cases include the COVID-19 hyper-inflammatory syndrome¹.

Persistent effects of COVID-19 including fatigue, dyspnea, chest pain, anxiety, depression and arthralgia, may last for months and lead to a decline in quality of life². This has also been reported for an increasing number of previously healthy individuals without co-morbidities, who did not require admission to the hospital, but continued to have persistent multi-organ symptoms months after COVID-19². The concept of so-called long COVID has gained ground in re-

cent months. Generally, long COVID consists of a wide range of recurring symptoms of different intensity and duration experienced by patients, affecting the respiratory tract system, brain, cardiovascular system, kidneys, gut, liver, and skin^{3,4}. Of note, pediatric data are scarce in the field. The aim of this mini review is to briefly summarize the existing data regarding this new clinical entity.

Epidemiology

In July 2020, the US Centers for Disease Control and Prevention reported that one in five patients aged 18-34 years old with a positive test for SARS-CoV-2 and without chronic medical conditions had not fully recovered 2-3 weeks later⁵. Similarly, according to other studies, one out of ten of COVID-19 survivors developed symptoms of long COVID⁶. In addition, an observational cohort study from 38 hospitals in Michigan, United States, evaluated the outcomes of 1,250 patients two months following discharge⁷. 6.7% of the patients died and 15.1% required re-admission. Out of the 488 patients who completed a telephone interview in this study, 32.6% reported persistent symptoms⁷. Similar findings were reported by a study from Italy⁸. Moreover, Greenhalgh et al⁹ concluded that up to one in 10 adults suffered prolonged symptoms up to 3 weeks following COVID-19.

The UK Office of National Statistics recently reported that 1 in 5 questionnaire respondents who tested positive for COVID-19 had symptoms for a period of 5 weeks or longer, whereas 1 in 10 reported symptoms for 12 weeks or longer⁶. However, in a UK preprint of a prospective cohort study of 4182 individuals, 4.5% of the population had persistent symptoms more than 8 weeks and 2.6% 12 weeks after the disease¹⁰. In a recent large cohort of 1733 patients in Wuhan, persistent

symptoms were present in 76% of patients 6 months after diagnosis¹¹.

With regard to the pediatric population, data are scarce. In a study from Sweden¹, five children with potential Long COVID-19 had dyspnea, heart palpitations and chest pain and four of them had headaches, difficulties concentrating, muscle weakness, dizziness and a sore throat. All children suffered from prolonged fatigue and 6-8 months later not all of them had improved and none had fully returned to school¹. In addition, data from the UK Office for National Statistics showed that nearly one out of 5 children less than 16 years old had at least one symptom more than a month after COVID-19 diagnosis¹. In a preprint from Rome, out of 129 children, less than half had completely recovered four months after the infection and nearly 25% had three or more symptoms that persisted for at least that long¹¹.

Clinical Manifestations

Long COVID syndrome is characterized by heterogeneity in symptomatology. Recovered individuals continue to complain of a multitude of symptoms after the acute phase of the disease. Many of the patients describe having symptoms for more than 100 days. Most of the patients will experience at least one symptom during their convalescent period¹². Worryingly enough, most “long-haulers” are disabled in various degrees. Some of them are unable to work, some others cannot manage daily tasks and others complain of sleep disturbances.

Carvalho-Schneider et al¹³ showed that individuals who had recovered from mild or moderate COVID-19 and had been discharged from hospital were also experiencing post-COVID-19 symptoms, sometimes with disabling features and inability to return to their normal life^{12,13}. Fatigue, muscle weakness, sleep difficulties, anxiety or depression are the most common symptoms, even 6 months after disease onset¹⁴. The main symptoms of long-COVID as described in adult studies are shown in Table I.

Computed Tomography (CT) Findings in Patients with Long COVID

Chest CT plays a crucial role in the diagnosis and follow-up of patients suffering from COVID-19 pneumonia and its prolonged symptoms. Nevertheless, more long-term follow-up studies are needed to further elucidate the role of chest CT in this subset of patients.

According to recent publications, 94% of hospitalized patients have persistent lung CT findings. In a study by Han et al¹⁵, 35% of patients who recovered from severe disease developed fibrotic-like changes in the lung within 6 months. Some of these patients complained of sustained respiratory symptoms and 26% revealed pulmonary diffusion abnormality. In another retrospective study of COVID-19 patients 8 weeks after hospital discharge, 25% showed signs of early fibrosis¹⁶. Zhao et al¹⁷ have described radiologic abnormalities 3 months after hospital discharge. Ground-glass opacities, interstitial thickening, and crazy-paving patterns were also found at follow-up imaging in these patients.

Table I. Main symptoms of long COVID in adults.

Study (year)	Graham et al ⁴ (2021)	Huang et al ⁴ (2021)	Lopez-Leon et al ¹⁸ (2021)	Xiong et al ²² (2021)	Carfi et al (2020)	Dennis et al ²³ (2020)
Number of patients	100	1733	47910	538	143	201
Mean age(years)	43.2	57	17-87 (min-max)	52	56.5	44
Country	USA	China	NA	China	Italy	NA
Symptoms						
Brain Fog	82%	NA	NA	NA	NA	NA
Headache	64%	NA	44%	NA	NA	NA
Anosmia/Dysgeusia	74%/64%	NA	23%	NA	NA	NA
Myalgia	60%	63%	NA	13.4%	NA	NA
Generalized aches	40%	NA	11%	NA	27.3%	78.1%
Chest pain	38%	NA	16%	26%	21.7%	73.1%
Fatigue	84%	63%	58%	26.8%	53.1%	98%
Depression/anxiety	40%	NA	13%	NA	NA	NA
Shortness of breath	28%	NA	24%	NA	43.4%	NA
Insomnia/Sleep difficulties	36%	26%	11%	NA	NA	NA

The above-mentioned abnormalities may explain some of the respiratory symptoms reported by “long-haulers”. However, it is worth noting that so far, no specific imaging findings have been described in the cerebral parenchyma that could explain other long-COVID symptoms such as anxiety, sleep and concentration disorders.

Risk Factors-What do We Know So Far?

Risk factors for long COVID are currently not well defined¹⁸. Carvalho-Schneider et al¹⁹ have proposed severe acute disease as a possible risk factor¹⁹. In October 2020, the Tony Blair Institute for Global Change identified specific characteristics among long-haulers²⁰. Age seems to play an important role. Long COVID affects around 10% of patients 18-49 years old and 22% of those over 70 years old, suggesting an increasing risk with age. Furthermore, the age group of 40-59 years old shows a significant predisposition to long COVID. According to some studies, individuals between 30 and 70 years of age comprise 72% of cases¹⁴.

Gender also seems to be a risk factor for long COVID. Women are more likely to suffer from long COVID than men, especially those at working age (mean age: 45)¹⁴.

In addition, co-morbidities, functional status and physical activity prior to the disease onset appear to influence the development of long COVID¹². Hyperglycemia, cardiovascular and renal disease, and glucose-lowering agents that improve metabolic function are included in the factors associated with long COVID²¹. Vitamin D deficiency and obesity also seem to play a significant role in developing long COVID symptoms²¹. It has been hypothesized that long COVID in individuals with co-morbidities might trigger the exacerbation of the co-morbidity itself. Therefore, close monitoring is recommended. A study by Xiong et al²² recommends long-term follow-up also for recovered patients who are asymptomatic.

While some risk factors for long COVID have been described in adults, so far there is lack of data for children. It appears that COVID may occur in previously healthy children^{1,11}.

Concerns and Future Perspectives

Multi-organ involvement is being reported by increasing number of patients with long COVID^{23,24}. The remarkable diversity of symptoms in patients with long COVID raises questions regarding the underlying mechanisms in-

involved and how these symptoms relate to future health outcomes. Identifying those at risk for long COVID is yet another challenge⁵.

Long-term fatigue is not uncommon after other viral infections also. Similar persistent symptoms have been described following severe acute respiratory syndrome and Middle Eastern respiratory syndrome illness, although for the latter they have been described only in patients with severe disease²⁵. When Lam et al²⁶ followed up 369 survivors of severe acute respiratory syndrome four years after they developed the disease, fatigue was documented in more than 40%. Nonetheless, long COVID appears to be different in that a variety of symptoms have been reported and that they either persist or develop after withdrawal of initial symptoms. Also, several people in the same family experience long COVID, which may suggest that genetic or environmental traits might predispose individuals to this entity²⁶.

Whether long COVID is a unique condition, or it may involve more than one discrete pathology also remains to be clarified. The variability of the related symptoms makes the existence of a unique causative pathogenetic mechanism unlikely. One could argue that long COVID symptoms are categorized into two groups; those of clearly organic etiology, such as anosmia, dysgeusia, shortness of breath, and non-specific symptoms, i.e., headache, generalized aches, fatigue, depression, anxiety, insomnia and sleeping difficulties. The organic etiology of the latter is questionable. It might be that not all symptoms characterized as “long COVID” are related to somatic involvement, but some may reflect loss of psychological reserves. The psychological implications of the COVID-19 pandemics an aspect that should not be underestimated. The high mortality rate, the unprecedented measures taken to control the spread of the disease and the pervasive uncertainty around the outcome of the disease have caused significant long-term psychological distress in the general population since the outbreak of the epidemic. On top of that, social isolation during the disease, particularly in individuals who required hospitalization, and the anxiety caused by severe and potentially fatal somatic symptoms, may have added to the pre-existing psychological burden in those who experienced physical illness.

Children are possibly not exempt. Taking into consideration that childhood is critical for the acquisition of social, behavioral and educational development, children can be naturally overwhelmed by the stress caused by the pandemic

in general but also by physical illness. Hence, long-lasting effects of the disease may not be solely attributed to direct viral actions on different organs. The identification of long COVID in the pediatric population highlights the need for a deeper understanding of the impact of the pandemic on children's future health despite the low incidence of severe disease in this population¹¹.

Conclusions

Surviving the acute COVID-19 disease is not the end of the story as survivors may experience and suffer from ongoing symptoms¹². The existing evidence that COVID-19 can have long-term effects, the so called Long COVID, underscores the need for a multidisciplinary approach. This includes the involvement of internal medicine physicians, neurologists, pediatricians, but also psychologists, psychiatrists and mental health experts in order to monitor closely affected patients and implement measures to reduce the impact of the pandemic on the overall patient wellbeing.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

No funding was received for this work..

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