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Prolonged illness after COVID-19

PERSPECTIVES

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Even patients with an initial mild course of COVID-19 report persistent symptoms, including chest pain, shortness of breath, headache and fatigue. Many have a reduced quality of life. We do not yet have an overview of the long-term effects of the pandemic.

As of September 2020, more than 33 million people in 235 countries have been infected with SARS-CoV-2 and developed COVID-19 (1). The number of reported deaths is around 995 000 (as of 28 September 2020), and the pandemic and its consequences continue to spread. The symptom profile of COVID-19 varies markedly, from an asymptomatic condition to symptoms such as fever, cough, shortness of breath, chest pain and fatigue, as well as neurological symptoms such as loss of sense of taste and smell, and abdominal pain and other gastrointestinal symptoms. Serious courses of the disease requiring hospitalisation and treatment in an intensive care unit are well described in the literature (2–10).

The different courses of the disease are characterised by dysfunction in vital organ systems, primarily the lungs (acute respiratory distress syndrome, ARDS), but all organ systems can be involved due to immune and coagulation activation. However, the long-term course of COVID-19 in patients who initially experienced mild symptoms in the acute phase is less well known, especially in people who are not hospitalised.

Prolonged illness relatively common

It has been reported that 10–33 % of people experience prolonged illness (several weeks and months) after being infected with COVID-19, and that women are twice as prone to this as men (11–13). There is still uncertainty about the extent of the long-term symptoms after the acute phase because COVID-19 is new and there is therefore no long-term data. In addition, the actual number infected with COVID-19 is assumed to be much higher than the reported figure. Various follow-up studies are underway, but most only include hospital patients. Many people with COVID-19 have self-isolated at home based on the clinical course without having been tested, since the testing capacity was inadequate up until a few months ago. These people are less likely to be included in follow-up studies. A recently published study found that certain symptom complexes were associated with an increased risk of developing long-term symptoms. If the patient had a combination of persistent cough, hoarseness, headache, shortness of breath and significant loss of appetite during the first week of COVID-19, the likelihood of subsequently experiencing long-term symptoms increased two- to threefold (14).

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Other viral infections have been shown to cause long-term sequelae (postviral syndromes), however little is known about the long-term effects of COVID-19 and few studies have been conducted. The extent to which other postviral syndromes can be extrapolated to COVID-19 patients is also uncertain (15). There are an increasing number of reports of long-term courses of COVID-19. Some of these descriptions are by doctors who have had the disease themselves and have reported long-term symptoms after the acute phase (16–18). Others cover larger populations (11), (19–20).

In a survey of both hospitalised and non-hospitalised COVID-19 patients with confirmed SARS-CoV-2, respondents were contacted 14–21 days after testing. Approximately one third (36 %) of the non-hospitalised patients indicated that they had not returned to their normal condition. The most common symptoms were pleuritic pain (74 %), fatigue (70 %), headache (62 %), cough (62 %), body aches (58 %), fever (55 %), chills (52 %) and loss of sense of taste and smell (52 %) (11). In another recently published article from Italy, researchers describe persistent symptoms in a population of 143 patients who were

followed up for an average of 60 days after hospitalisation for COVID-19 (19). Only 18 (12.6 %) of these patients had been treated in an intensive care unit, so most had a non-serious acute course. A total of 21 patients (15 %) received non-invasive ventilation and 7 patients (5 %) received invasive ventilation. Of the 143 patients, only 18 (12.6 %) were completely free of any COVID-19-related symptoms. A significant proportion reported continued fatigue (53 %), shortness of breath (43 %), joint pain (27 %) and chest pain (22 %). Forty-four per cent of the patients also reported a reduced quality of life.

Symptoms involving the heart

Puntmann et al. performed cardiac examinations on a cohort of 100 patients who had recently had COVID-19 (20). Sixty-seven per cent of the patients had never been admitted to hospital in connection with the acute phase of the disease. The median time interval between confirmation of COVID-19 and the study was 71 (64–92) days. The patients underwent an MRI examination of the heart, which showed myocardial affection in the form of reduced ejection fraction, higher left ventricular volume, increased right and left ventricular mass, and elevated T1 and T2 values in 78 patients (78 %). Sixty patients (60 %) had an ongoing myocardial inflammatory condition. In addition, elevated troponin T was found in 71 (71 %) patients. Those with significant affection were also given an endomyocardial biopsy, which showed active lymphocytic inflammatory condition. These findings were independent of the initial severity of COVID-19 and the time from diagnosis to imaging. It must be emphasised that this study had no control group as it was solely an observation of a group of patients who had had COVID-19.

> ***«COVID-19 manifests as a long-term disease in some people, including those who have experienced a mild acute infection and those in the younger age groups»***

The long-term disease courses appear to have a cyclical nature, where the intensity of symptoms first decreases and then increases again (13, 21). It is unclear whether these symptoms are a consequence of reinfection, reactivation of the virus or an immune response (22). It is becoming increasingly clear that COVID-19 manifests as a long-term disease in some people, including those who have experienced a mild acute infection and those in the younger age groups (11), (19–20), (23). This can have implications for employment in terms of long-term sick leave. The long-term symptoms can have a major effect on quality of life, they will require a multifaceted follow-up and the socioeconomic consequences may be significant. An interdisciplinary collaboration will be needed to facilitate rehabilitation and an individually tailored return to work.

The Advisory Board for Rehabilitation in South-Eastern Norway Regional Health Authority has devised a patient care pathway for the rehabilitation of patients admitted with COVID-19 in the specialist health service (24). Both Sunnaas Rehabilitation Hospital and Vestfold Hospital Trust are already

rehabilitating COVID-19 patients. However, the service is currently aimed at previously hospitalised COVID-19 patients. Those with long-term symptoms who were not hospitalised and those who experienced an acute phase of the disease but were not tested may risk falling between the cracks. Another potential pitfall is that there is very little reliable knowledge on long-term illness with COVID-19. Some doctors may therefore be somewhat dismissive of such patients, but a comprehensive and pragmatic approach needs to be taken, focussing on symptom management and prevention of overdiagnosis (12, 23).

Many unanswered questions

There are still many unanswered questions: Why are some people asymptomatic, while others have a fatal outcome? Why do some people go from a mild course to a long-term illness, while others with a serious infection seem to avoid long-term effects? There is an urgent need for follow-up studies using a wide range of approaches, including a thorough mapping of physical status, organ function, cognitive and emotional dysfunction, and immunological response of both the innate and acquired immune system, as well as genetic studies that identify possible patterns that can shed light on the more complicated courses of the disease.

> ***«The long-term symptoms can have a major effect on quality of life, they will require a multifaceted follow-up and the socioeconomic consequences may be significant»***

It is still unclear whether all of those with long-term symptoms will recover 100 % or whether a certain proportion will have lingering residual symptoms (12). It is hoped that these patients will eventually make a spontaneous recovery with the help of comprehensive support, rest, symptomatic treatment and a gradual increase in activity.

At present, there is no systematic knowledge on the long-term effects of COVID-19. The reports we have about the variable manifestations imply that individuals can experience different sequelae, but that the connection between these and the course of the disease is still uncertain. In order to avoid unnecessary discussions based on lack of knowledge, it is crucial that our knowledge of long-term effects is founded on research. Most COVID-19 patients experience a short course of the disease and have a very good prognosis. However, a small proportion bear the heavy burden of long-term effects, and it is this group that needs increased focus. The last chapter on COVID-19 has yet to be written.

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