LONG COVID – THE GIFT THAT KEEPS GIVING

Michael Graz, Biophys Ltd, UK

Heather Graz, Biophys Ltd, UK

Bryan Hanley
ACTA (ACTA is the joint Dental Faculty of the University of Amsterdam and the VU Amsterdam). A.B.Hanley@acta.nl

Following on from Professor Charles Bangham's treatise on long COVID in this Science in Parliament in Summer 2021 (77(2), 16-18, 2021), a review of what is now known about long COVID, 2 years later was warranted.

WHAT IS LONG COVID?

Long COVID (also known as post-COVID syndrome and post-acute sequelae of SARS CoV-2 infection (PASC)) manifests as a set of clinical symptoms that are reported by people who have had COVID and are still reporting effects some months after the initial infection. A range of symptoms have been reported and the effects vary between individuals both in severity and in the length of time that they persist. It is estimated that between 10% and 30% of people who are infected with COVID develop long COVID [1] and that, while some symptoms appear more often than others including tiredness or fatigue that interferes with daily life symptoms that get worse after physical or mental effort and fever [2]. Other symptoms seem to target specific parts of the body and cause heart palpitations, shortness of breath, exercise intolerance, difficulty in thinking or concentrating (brain fog), headaches, fatigue, muscle weakness, sleep disturbances, diarrhoea and stomach pain and (chronic) joint or muscle pain [1]. The symptoms are similar to those reported by people with myalgic encephalomyelitis/ chronic fatigue syndrome

(ME/CFS) and other poorly understood chronic illnesses that may occur after other infections.

WHAT CAUSES LONG COVID?

One of the problems with long COVID is that there is no single test available that can confirm a diagnosis. Even a history of having had (or not had) COVID is not definitive since some people who develop the symptoms associated with long COVID can have had asymptomatic COVID (around 20% of people who have COVID are largely or completely asymptomatic perhaps due to pre-existing T cell immunity) and were not aware of having the infection in the first place. In addition, there is no mechanistic basis for diagnosis of long COVID [2]. The incidence of long COVID is estimated at 10–30% of non-hospitalized cases, 50–70% of hospitalized cases and 10–12% of vaccinated cases [3]. It is, therefore, inaccurate to suppose that vaccination can completely eliminate long COVID. Symptoms of long COVID can persist for years [4] and, in some cases it is estimated that these may last a whole lifetime [5]. For affected individuals, the consequences of long COVID are significant and a return to normality (e.g. working and leisure pursuits) may be impaired for a considerable time [6].

A number of possible mechanisms for long COVID have been suggested, based in part on other viral diseases, the characteristics of the disease and those of ME/CFS and the organs affected. These include the accumulation of the virus in tissues and a failure to eliminate it from the body, reactivation or increased susceptibility to other viral infections, immune dysregulation, effects on the microbiome and, somewhat intriguingly, priming of the immune system by molecular mimicry [7]. Some recent work has linked long COVID to disruption in serotonin signalling driven by Type I interferons [8]. Immune dysregulation has been observed in those with severe and persisting COVID and it was speculated that this was due to gut fungal pathobionts (opportunistic microbes that emerge as a result of perturbations in the healthy microbiome) [9]. A key aspect in the development of long COVID appears to be the need to take time to rest and recover from the initial infection and this in turn means that those who are more economically vulnerable might suffer more longer-term effects [10].

RESEARCH INTO LONG COVID

While COVID is, for many, a problem for which we have found a solution (vaccination), it remains a significant health issue for many – particularly those with pre-existing conditions. Health authorities would like COVID to be considered as small a risk (in the perception of the general population, at least) as seasonal flu. It should be noted, however, that seasonal flu still kills about 15,000 people a year in the UK [11]. In the UK the National Institute for Health Care Research (NIHCR) have a programme of work on long COVID and have recently implicated the migration of a certain type of immune cells in the development of long COVID respiratory symptoms [12] and other work is funded in the UK [13] to develop new treatments. While much of this work is designed to assess the prevalence of long COVID, an understanding of the causes will be essential if effective treatments are to be developed.

In the US, the National Institutes of Health (NIH) are funding a number of studies including the RECOVER initiative ($1.15Bn) [14]. The aim of RECOVER is to "rapidly improve our understanding of and ability to predict, treat, and prevent PASC (post-acute sequelae of SARS-CoV-2), including Long COVID." Such work is still at an early stage and recent investigations are still at the stage of attempting to develop a framework for identifying long COVID based on symptoms and to thereby define long COVID as a new condition [15]. Although the NIH is in the assessment phase of studies into long COVID, they are also funding clinical studies under the RECOVER program to try to discover treatments that may be effective based upon what we already know about the virus [16].

SOCIETAL IMPACTS OF LONG COVID

The societal impacts of long COVID are still difficult to quantify. It is likely that progression to the development of long COVID will remain at between 5 and 10% of those infected with the virus. Since it has been estimated that 10% of people who develop long COVID are affected to the extent that they stop working while others are off sick for extended periods and, once they return to work, their effectiveness will be reduced due to fatigue, the potential societal and economic impact is severe [17].

Finally, all of the above makes two key assumptions:

1 That new variants of COVID or other viral respiratory diseases (which will almost certainly arise) do not lead to a greater incidence of long COVID than the 10% figure quoted above.

2. That long COVID does not increase the prevalence, susceptibility to or severity of other conditions such as other viral infections or other organ-related diseases such as respiratory disease, immune function disruption or cardiovascular disease.

Based upon what we know and have learned over the past 3-4 years, we cannot have complete confidence about either of these assumptions. There are already some indications that a proportion of individuals who suffered from severe COVID are suffering from multi-organ damage [18] and, while this may not be due to persistence of the virus it is, nonetheless, a long term consequence of infection and is, therefore a type of 'long COVID'.

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