COVID-19: not just an acute illness

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Some people with COVID-19 will need support for physical, emotional and mental symptoms long after they have recovered from the acute phase of the infection. Many of those with so-called ‘long Covid’ are likely to have a post-viral condition very similar to chronic fatigue syndrome/myalgic encephalomyelitis for which management guidelines and a network of NHS clinics already exist.

COVID-19 (SARS-CoV-2) was declared a global pandemic in March 2020 and by October 2020 there were over 40 million confirmed cases and over a million deaths worldwide. SARS-CoV-1 caused a similar acute illness in 2003, but it was a self-terminating epidemic resulting in only 8096 cases and 774 deaths.

Obtaining clear epidemiological information on the symptomatology of COVID-19 is difficult, especially as the majority of infections are asymptomatic or cause only mild symptoms, and many of these cases will never be identified. The US Centers for Disease Control (CDC) current best estimate is that 40% of cases are asymptomatic. In the UK, as of 17 October, there were 705 428 positive COVID-19 tests, 152 239 admissions to hospital and almost 50 000 deaths (depending on which definition of COVID-19-related death is used). Most of the hospitalisation is due to pulmonary symptoms and requirement for supplementary oxygen and other respiratory support.

As such, there has never been a suggestion that viral infection with SARS-CoV-2 becomes chronic (like, for example, hepatitis B and C, HIV and herpes viruses). However, it has become clear from the early days of the pandemic that not everyone who survives COVID-19 infection goes on to make a rapid, uncomplicated recovery. There is no internationally accepted definition of the condition where symptoms persist for longer after a COVID-19 infection than one would anticipate after a ‘normal’ acute viral illness. In the USA, a common term is ‘long haulers’, while in the UK the common term is ‘long Covid’.

A recent review suggested the use of the term ‘post-acute Covid’ for symptoms lasting more than three weeks after onset of symptomatic disease, and ‘chronic Covid’ for those...
where symptoms persisted for more than 12 weeks, may be a useful working definition. NICE, SIGN and the RCGP, on the other hand, have recently published a guideline that uses the term ‘Post-COVID-19 syndrome’ for cases where symptoms persist for more than 12 weeks after infection.\(^6\) This search for a definition is more than just semantics, as a working term will clearly be necessary if good epidemiological information and research is to be generated.

**Confirming the diagnosis**

Many cases of long-Covid will develop after relatively mild acute symptoms and, in some cases, it may not even be possible to confirm in a laboratory test that the individual had SARS-CoV-2 infection. There are two ways of testing for infection: either by looking for viral RNA in a throat/nasal swab using a technique known as polymerase chain reaction (PCR), or by detecting antibodies to the virus in the bloodstream using a variety of established immunological techniques. Both of these tests have limitations as infection control tools, but a positive PCR or antibody test will confirm exposure to the virus.

However, viral RNA may only be detectable for a few days after infection and viral antibodies may only be detectable for a few months (or even less – although protective immunity will persist for longer as it is mediated by immunological mechanisms other than antibody). This has been an issue for some patients who believe that their symptoms have been triggered by coronavirus but have been unable to prove it with a positive test.

**The clinical syndromes**

It seems that there are three patterns of protracted symptoms initiated by infection with SARS-CoV-2. It has been known for many years that anyone who survives a critical illness that precipitated admission to an intensive care unit (ICU) is at risk of developing a constellation of physical, mental and emotional issues that are often referred to as post-intensive care syndrome (PICS). The physical symptoms include muscle weakness, fatigue, reduced mobility and breathlessness. There are significant cognitive difficulties such as reduced memory, poor concentration and reduced ability to organise thought and problem solve. Finally, there are a number of emotional/mental health issues such as anxiety/depression, reduced motivation and ‘flashbacks’ (reminiscent of post-traumatic stress disorder).

Secondly, in line with other severe infections such as pneumonia or sepsis, there may be specific end-organ damage that occurs as a result of the infection itself. Severe lung involvement (the hallmark of SARS) may result in pulmonary fibrosis, acute kidney injury may give rise to chronic kidney disease. Neurological damage may also be caused, and myocarditis may lead to cardiomyopathy. All these sequelae have been described with COVID-19 infection, and there seems to be a particular predilection for COVID-19 infection to produce thromboembolic problems and long-term kidney damage.

However, although data are currently limited, it seems likely that the overwhelming majority of long-Covid cases will be post-viral chronic fatigue syndrome (CFS) rather than PICS or specific post-COVID-19 end-organ damage. This has certainly been described in many cases and, unlike the other two syndromes, it has been described in cases of very mild disease and in instances when the diagnosis of SARS-CoV-2 infection has not even been definitively established.\(^4,5\)

The condition of chronic fatigue syndrome/myalgic encephalomyelitis (CFSME) has been recognised for many years and it remains largely unexplained.\(^7\) There is a very clear and repeated pattern of symptoms that allow a positive diagnosis to be made but, despite intensive research, there is no unifying biomedical mechanism to explain the symptoms. Many cases of CFSME seem to be triggered by infection but, despite speculation, no single infecting agent has ever been specifically implicated as causative.

The cardinal feature of CFSME is disabling fatigue, specifically exacerbated for a prolonged period by activity.\(^7\) This is often referred to as post-exertional malaise or ‘payback’. Another prominent aspect is the collection of cognitive problems frequently grouped together and referred to as ‘brain fog’. These include difficulties with concentration, memory and word finding (not dissimilar to the cognitive issues seen with PICS).

Other common issues include unrefreshing sleep, myalgia, arthralgia, poor body temperature control and intermittent autonomic symptoms (tachycardia, postural hypotension, etc). All these features were seen in a group of post-SARS survivors following the 2003 SARS-1 outbreak,\(^8\) and it is well accepted that SARS-1 led to a significant incidence of CFSME.

**Diagnosis and management**

The diagnosis of non-COVID-19 CFSME is often said to be one of exclusion, but in practice the features described above are so characteristic that they permit a positive clinical diagnosis and only require a few simple laboratory tests to exclude other potential conditions.

Most of those with prolonged symptoms after a COVID-19 illness will be managed in primary care and useful guidelines for management have been published.\(^9\) Clearly only those who have been on a critical care unit will be at risk of PICS and it is most unlikely that those with mild symptoms who have not been hospitalised will have suffered end-organ damage such as pulmonary fibrosis. Therefore, the vast majority will be suffering from post-viral CFSME. There is no reason to think that this should differ substantially from the CFSME seen after SARS-1, nor indeed from that seen after any other viral infection.
The important thing is that clinicians listen to patients, believe their stories and reassure them that their symptoms are real and due to a physiological cause – albeit one for which the basic mechanism remains unidentified. It is important that patients make compromises in their recovery and steer a middle ground between ‘pushing themselves too hard’ and partaking in negligible activity. For complex cases, referral to a local CFSME clinic will allow them to be assessed by a multidisciplinary team that will be able to exclude alternative pathologies by appropriate investigation and supervise rehabilitation by properly trained therapists.

In common with many other chronic diseases such as malignancy and inflammatory conditions, a supportive approach with cognitive behavioural therapy (CBT) can be helpful – and this in no way implies that the ‘symptoms are all in the mind’. Similarly, a measured increase in activity under close supervision, to achieve the compromise discussed above, may also be useful. The British Association for Chronic Fatigue and ME (BACME) has produced useful guides for management of symptoms and therapeutic approaches in CFSME, and much of their advice would be relevant to protracted symptoms after COVID-19.8,9,10

**Summary**
The current COVID-19 pandemic represents a major challenge to healthcare systems, the economy and social fabric of most of the globe. Although the major focus has been on the small proportion of infected individuals who develop severe and life-threatening respiratory illness that requires intensive care, it is evident that prolonged symptoms after apparent recovery from acute COVID-19 infection are becoming a concerning feature of this pandemic. It is too early to say just how common ‘long-Covid’ will be, and what the prognosis for recovery is for affected patients. The majority of prolonged symptoms are almost certainly due to a post-viral chronic fatigue syndrome, indistinguishable from CFSME. A network of NHS clinics for the management of CFSME already exists and it would seem sensible to support this with enhanced resources rather than ‘re-inventing the wheel’ by establishing separate clinics.

**Declaration of interests**
Alastair Miller chaired the British Association for Chronic Fatigue Syndrome and ME (BACME) from 2013 until 2016. His views are his own and do not represent the official views of BACME nor of any other organisation. He has no financial conflict of interest.

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