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Chronic fatigue syndrome: an old public health issue highlighted by the COVID-19 pandemic

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"Oh I need a coffee! I am so tired!" Something would feel amiss if one does not hear this exclamation at least once on a workday. More often than not a cup of coffee is exactly what you need to help you focus, be it the third paper on a Monday morning or the patient rounds that have made your eyes heavy. However, for some people 'tired' could mean not being sure if they could make it to the post box or being too exhausted to stand long enough to take a shower or even answer a simple phone call, all of it despite enough number of hours spent sleeping. Such severe examples are gaining more attention in the wake of the ongoing COVID-19 pandemic that hit the world in March 2020. Fatigue is a major symptom associated with long COVID, but what does it entail?

If an average adult in our society were to attempt to run a marathon, they would most likely, not make it without prior training. The result of any serious attempt at that would most probably be fatigue, i.e. a reduced ability to activate muscle force or power leading to weaker muscle response.[1] Exercise induced peripheral fatigue is determined by a multitude of factors including local factors such as pH level, ion distribution, as well as oxygen supply and consumption e.g. through mitochondria.[1–5] Decreased muscle perfusion e.g. due to an NO-deficiency caused by oxidative stress or aging can lead to accelerated fatigue.[3,6] Muscle oxygenation and perfusion are also influenced by systemic factors like hormonal signalling, the ability to reoxygenate blood through an intact lung or the amount of breathing work, all of which are affected by COVID.[7–10] In addition, fatiguing locomotor exercise alters neuromuscular function, which in turn leads to reduced muscular activation and activity.[11]

While such fatigue i.e. exhaustion caused by physical activity can be relieved by resting, persistent fatigue that cannot be alleviated by sleep may indicate chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME). CFS/ME is a complex condition that affects multiple organ systems. Its symptoms can therefore be multifaceted and vary in severity. According to the new definition by the Institute of Medicine (now National Academy of Medicine (NAM)),

USA, to be diagnosed with CFS/ME, a patient must exhibit three main symptoms: (1) A substantial inability to perform pre-illness levels of activity that lasts for more than 6 months. This should be accompanied by profound fatigue of new onset that is not a result of unusual cognitive, physical, emotional or social exertion and is not significantly relieved by rest. (2) Post-exertional malaise (PEM) after an activity that would not have been an issue before the illness. Symptoms worsen after activity with a delay of hours or even days and a recovery time that is disproportional to the activity itself (hours to weeks). (3) Unrefreshing sleep despite the absence of objective alterations in sleep. Other than these, at least one of two additional manifestations must be present: (1) cognitive impairment (aka "brain fog") that exacerbates by exertion and (2) orthostatic intolerance, in which a patient develops symptoms such as increased heart rate and blood pressure abnormalities while in an upright or standing position.[12]

In some cases, COVID-19 has been shown to cause both acute as well as prolonged neuropsychiatric manifestations, possibly due to CNS immune cell activation.[13,14] Between 13 and 23% of hospitalized COVID-19 patients suffer from fatigue and PEM-like symptoms more than 6 months after the infection.[15] These numbers, although alarming, are hardly surprising. Looking back at the 2002/03 SARS pandemic, a similar proportion of hospitalized patients with a severe course also developed CFS/ME (27% of survivors 4 years after hospitalisation).[16] Other common pathogens that can lead to CFS/ME include viruses like Epstein-Barr virus (EBV), cytomegalovirus (CMV) and enteroviruses, bacteria such as mycoplasma, *Borrelia burgdorferi* (Lyme disease), and *Coxiella burnetii* (Q fever).[17] In fact, in 3 out of 4 cases of CFS/ME, the disease develops following an infectious episode.[18] Interestingly, the innate immune response to infections is generally higher among women than men, which could perhaps also explain the higher prevalence of CFS/ME among women given the role that immunity plays in it. With an estimated prevalence of 0.1-0.7%, CFS/ME is far above the threshold value set by the European Union for classification as a rare disease (<5:10,000). [19–

[21] In Germany, its prevalence was comparable to multiple sclerosis (MS, ~300,000) before the COVID-19 pandemic.[18] CFS/ME is also associated with a considerable burden of disease. In terms of individual burden of disease as measured by health-related quality of life, it scores lower than not only MS but also chronic obstructive pulmonary disease (COPD) as well as stroke.[22] Another measure that looks more into the socioeconomic burden of disease is 'disability-adjusted life years (DALY)' that also takes incidence into account. People with CFS/ME lose more DALYs than patients of MS as well as other debilitating conditions such as epilepsy or Parkinson disease.[23]

Despite the worryingly impressive numbers, CFS/ME remains poorly understood. A review paper written in the 1970s by two psychiatrists in the United Kingdom concluded because of the absence of physical signs and the higher prevalence in women that a psychosocial aetiology of CFS/ME was most likely. This work shaped pathophysiological understanding in the years that followed.[12] However up until recently, research remained largely focused on psychological, psychosomatic, or social aetiology and consequently treatment programs focused on cognitive behavioural therapy or activating therapy to improve endurance. While these therapies were recommended by the National Institute for Health and Care Excellence (NICE), UK in their guideline published in 2007,[24] it has since been established that these approaches could actually exacerbate the disease. To date, there is no test or biomarker for objective diagnosis. Owing to this, CFS/ME often gets delegitimized as "not a real physiological condition" and patients often face stigma from their peers and healthcare professionals alike.[25] This further deteriorates the quality of life for people with CFS/ME, who are already experiencing trauma, grief and loss due to their severe symptoms, and could lead to the development of depression and a heightened risk of suicide.[26,27] Many patients, clinicians and experts associate the persistent stigmatization of the disease with the name 'chronic fatigue syndrome' and suggest that it should be referred to as 'myalgic encephalomyelitis' to underline the neuroimmunological character of the disease.

A public health problem of this magnitude certainly needs immediate attention and efforts are indeed being taken. The new guideline published by NICE in October 2021 has parted ways with the earlier, potentially harmful treatment recommendations.[28] With pandemic COVID-19 further highlighting the public health impact of CFS/ME and accelerating research, hopes are high for improved therapeutic approaches as well as a better understanding of the disease.

Conflict of Interest

There is no conflict of interest to declare.

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