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Editorial

A research agenda for post-COVID-19 fatigue

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1. Background

Now that the COVID-19 pandemic has been ongoing for almost two years, increasing attention is directed towards what is being called 'Long COVID' or 'post-acute sequelae SARS-CoV-2 infection' (PASC). Fatigue is one of the main symptoms of PASC [1]. Prevalence rates of fatigue persisting for months after COVID-19 onset range from 9% to 58% depending on time of follow-up, study population, recruitment method and in-depth evaluation [2–4].

Post-infective fatigue syndrome (PIFS) is defined as persistent, severe fatigue after an infection that cannot be explained by other medical or psychiatric conditions, which has been present for at least six months and significantly affects daily functioning [5]. PIFS is not unique to COVID-19. It has been reported after a diverse spectrum of infectious diseases, including but not limited to Q fever, Lyme borreliosis and SARS-CoV-1, where persistent illness and disability is recognised in 10–35% of adolescents or adults [6–8]. Factors predictive of PIFS include clinical and laboratory features indicative of the severity of the acute infection, and psychological factors such as the cognitive and behavioural responses to the acute illness [6,9]. The question why some patients develop PIFS whereas others do not, remains largely unanswered.

The COVID-19 pandemic provides a unique opportunity to investigate pressing questions with respect to the mechanisms that contribute to developing post-COVID-19 fatigue, thereby potentially helping answering unresolved questions regarding PIFS after other infections. The COVID-19 pandemic offers the opportunity to investigate these questions in large scale prospective studies among patients with known dates of infection onset. As COVID-19 is a worldwide pandemic it provides opportunities to investigate social and cultural factors contributing to PIFS. With these opportunities it is important to think about how to transfer knowledge from COVID-19 to foster our understanding of PIFS more broadly. Conversely, research on post-COVID-19 fatigue may benefit from insights from PIFS obtained in previous research.

2. Methods

This paper outlines research priorities for post-COVID-19 fatigue. In May 2021, an international workshop with experts in the field of PIFS was organized by COFFI, the International Collaborative on Fatigue Following Infection [10,11]. Participating experts presented current knowledge about PIFS within their respective disciplines. Furthermore, they formulated research questions that, from their field of expertise, need to be addressed to foster our understanding of post-COVID-19 fatigue specifically, and PIFS in general. The following three research categories were identified as priorities.

3. Research priorities

3.1. Etiology of post-COVID-19 fatigue

3.1.1. Biomedical

Several biomedical theories about the etiology of post-COVID-19 fatigue have been proposed including: end-organ damage to the lungs or heart, ongoing aberrant cytokine activity, changes in skeletal muscle morphology and function, and neurological causes resulting from injury within the brain or peripheral nervous systems.

Longitudinal studies with nested case-control series using validated questionnaires and protocol-driven clinical and laboratory assessments to compare patients who recover uneventfully (controls) versus those who develop persistent fatigue (PIFS cases) are needed. The studies should apply multi-omics (genomics, transcriptomic, proteomics, metabolomics), and state of the art neuro-imaging, notably positron emission tomography (PET) with new generation tracers, to provide insights into mechanisms involved in development of PIFS.

Cardiovascular risk factors and pre-existing cardiovascular disease are associated with worsened adverse outcomes after COVID-19. Cardiovascular biomarkers indicating myocardial injury are frequently elevated in proportion to disease severity, and have been independently associated with poor outcome after COVID-19 [12]. Biomarkers that integrate information from several pathophysiological axes, including

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inflammation, may provide the strongest prognostic information and provide a link between comorbid disorders, such as cardiovascular, auto-immune and lung diseases, and post-COVID-19 fatigue.

The need for careful consideration of confounding factors is highlighted in the group of survivors of critical COVID-19 illness who were admitted to Intensive Care Units (ICU). They are at high risk of developing post intensive care syndrome, which can also feature chronic fatigue [13]. This raises questions on how COVID-19 ICU survivors differ from other ICU survivors, recognising that COVID-19 patients were usually admitted to the ICU for a longer time than non-COVID-19 patients [14]. Is fatigue more common after COVID-19 than after other ICU-indications?

3.1.2. Psychosocial

Social factors related to the pandemic, such as restrictive public health control measures may have had a negative impact on the psychological well-being of patients required to stay in isolation while recovering from COVID-19. Further, for many patients it was terrifying to suffer from an illness with initially unknown, and then high publicized substantive mortality rates [15]. That social and cultural factors can influence the functional outcome of many disorders is not in doubt. The question is whether and how this applies to COVID-19. Studies on post-COVID-19 fatigue conducted in Europe have reported remarkably higher prevalence rates of fatigue compared to studies from China [16]. This raises questions about possible cultural differences in the experience and/or reporting of fatigue. The global nature of the epidemic provides opportunities for investigating these differences. In addition to quantitative studies, qualitative studies can provide insight in how post-COVID-19 fatigue is experienced in different cultures, settings and age groups.

Previous research has shown that psychosocial factors, such as distressing life events, may predispose to developing PIFS, whereas symptoms of depression or anxiety, cognitive factors (i.e., illness beliefs) and behavioural factors (i.e., changes in activity patterns) may act as perpetuating factors [6,17]. It is therefore unfortunate that there seems to be opposition to research into psychosocial predisposing and perpetuating factors that play a role in PIFS. At the moment little research is done into the role of psychosocial factors in post-COVID-19 fatigue. However, we propose that experts in all areas work together with the aim of understanding the syndrome and helping patients as best as possible. It would be a shortcoming if we were to exclude research areas.

3.1.3. Additional questions

Further unanswered questions include: what are the symptom clusters of post-COVID-19 fatigue and do they differ from other PIFS symptom clusters. Are there specific subgroups to study regarding post-COVID-19 fatigue? Does the etiology of post-COVID-19 fatigue differ between virus variants? What is the relationship between exercise capacity and PIFS? What is the contribution of cardiovascular, respiratory and musculoskeletal impairments to post-COVID-19 fatigue? What is the role of vaccination?

Large prospective studies with long follow-up periods including both initially hospitalised and community-based patients are needed to capture the spectrum of acute disease severity. Generalisation will always be easier when studies are able to include population and primary care samples, and not solely those seen in secondary care, with the most severe symptoms. In mild to moderate illness, psychosocial factors can confound help-seeking, leading to overestimates of any observed links between a condition and psychosocial distress or previous vulnerability in all research. The use of previously validated instruments, such as the Chalder fatigue scale [18] or Checklist Individual Strength [19], to measure fatigue is strongly recommended.

3.2. Impact of post-COVID-19 fatigue on daily functioning and health economic outcomes

Post-COVID-19 fatigue is expected to have a profound impact on daily functioning, including work ability and quality of life. It is also expected to have economic implications due to increased absenteeism and health care consumption, as was previously shown among patients with infectious diseases other than COVID-19 [20,21]. Given the global scale of this pandemic and the large group of potential patients, special attention needs to be given to how society as a whole will be affected.

3.3. Interventions

There are very few evidence-based interventions for PIFS. Behavioural interventions were effective in reducing symptom severity and improving functional capacity for PIFS and for similar chronic fatigue states unrelated to infection [22–24]. These interventions should be available to patients with post-COVID-19 fatigue, and be evaluated using both psychological and biological data in relation to response to treatment. Exercise therapy was previously found to be effective in chronic fatigue syndrome [25], but its effectiveness has not yet been studied in PIFS. Until now, the effectiveness of interventions have only been investigated among patients who were fatigued for prolonged time periods. The COVID-19 pandemic offers the opportunity to carry out research earlier in the natural history of these condition.

Further unanswered questions include: How can the development of post-COVID-19 fatigue be prevented? Which factors are potential targets for interventions to prevent or resolve post-COVID-19 fatigue? Is early intervention appropriate? In addition, we recommend development of simple screening tools for use in primary care to allow timely identification for patients in need of intervention.

4. Methodological challenges

COVID-19 infections have generally occurred in waves globally – partly attributable to emergence of new variants with increased transmissibility and virulence, and partly the rigor with which public health control measures were implemented and adhered to. In addition, the epidemic has witnessed rapid emergence of new or improved diagnostics, better understanding of risk factors for severe disease, and better therapeutics. These rapid changes are all likely to have affected the diagnosis, treatment, and experience of COVID-19 infection, but also act as confounders when differences are observed at both individual and population-level infection outcomes.

5. Conclusion

Although post infective fatigue appears unlikely to be unique to COVID-19, the scale of the affected population is unprecedented. The resources and possibilities now available to study post-COVID-19 fatigue can potentially improve our understanding and management of PIFS in general. This is a research opportunity we can't pass up.

Declaration of Competing Interest

The authors have no conflicts of interest to declare. Outside the submitted work, RMM reports personal fees from training in CBT for irritable bowel syndrome for Central and North West London NHS Foundation Trust, the University of East Anglia, and University of Southampton. She receives payment for consultancy to Mahana Therapeutics and is a beneficiary of a licence agreement with King's College London and Mahana therapeutics to bring Regul8 (to the NHS and other international markets).

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