BIOSCIENTIST
The Salford Biomedicine Society Magazine

Long COVID - Widespread impact

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Long COVID – The past and the present

In the previous issue of the 'Bioscientist Magazine,' Ruby Naylor-Adamson discussed the continuation of COVID-19 symptoms months after the initial infection, also known as 'Long COVID'. The article featured COVID-19 prevalence statistics, risk factors, and promising potential therapeutic approaches according to information available at the time of publication. With emerging research, more is being discovered about the long-term implications, as well as the genetic and environmental factors playing a role in the clinical presentations. This article will expand on the facts understood at the time and compare it with novel findings about this complex health condition[7].

Symptoms and prevalence – Novel insights

The list of symptoms has expanded to include neurological, digestive, musculoskeletal, mental, and dermatological manifestations, as of March 2023[9]. In the UK, the people at highest risk of long COVID are 35 to 69 years old females, people residing in deprived areas, social care workers, unemployed teenagers aged 16 and over, and people whose health condition prohibits them from leading an active life, with fatigue continuing to be the most common symptom[8].

Women are four times more susceptible to long COVID than men, however, men have higher mortality rates with acute infection, due to women's innately stronger immune responses as an adaptation to support pregnancy. Studies have shown that women have an increased IgG antibody production in the early phase of exposure, which can lead to longer-lasting inflammation if the levels are maintained at an all-time high. The inflammatory marker IL-6 is increased, even months after infection[4]. In addition, female immune T-cells are more active than male T-cells due to large, upregulated expression of peripheral blood mononuclear cells[1]. This hyperactivity introduces a risk of developing autoimmune conditions, which is a known connection to long COVID. The cardiopulmonary symptoms are more severe in females, as SARS-CoV-2 infection impairs post-exercise control of heart rate and total lung capacity, which further enhances the feeling of dread and tiredness. This contributes to fear of unemployment, as women become chronically exhausted. Women have reported an 83% increase in depression rates compared to 36% of men, highlighting serious psychological disturbances caused by COVID. Note that these reports can be subject to bias and misrepresentation because of gender disparities in reporting concerns[4].

Autoantibodies

SARS-CoV-2 infection is characterised by heightened levels of pro-inflammatory cytokines as well as expression of specific chemokines which recruit neutrophils and monocytes to maintain inflammation. The pattern of chemokine antibodies in COVID correlates to the severity of the condition. A recent study from

DOI: https://doi.org/10.57898/biosci.56

Muri et al. (2023) showed that the monoclonal antibodies taken from COVID-19 convalescents bound to the chemokine impaired cell migration, and since the chemokines modulate immune cell trafficking, they also modulate the inflammatory response. Through examining 3 independent COVID-19 cohorts' plasmas, scientists found that the appearance of autoantibodies against specific chemokines helped identify acute and long COVID individuals. They have also found that high expression of specific chemokine antibodies was associated with favourable disease outcomes, and the autoantibodies against chemokines were omnipresent after SARS-CoV-2 infection. The derived from patient plasma samples monoclonal antibodies blocked leukocyte migration. There was a weak negative correlation between the age of the patient and their sum of all chemokine IgG reactivities. There were no significant differences in the COVID-19 specific chemokine antibodies between genders. Post-COVID, autoantibodies against these chemokines did not match the antibodies against the virus. Unsurprisingly, the spike receptor binding domain antibodies were significantly in unvaccinated convalescents, compared to those who received at least one dose of mRNA-based vaccine. Contrastingly to natural infection, there was no notable change in antibody reactivity to these chemokines upon the mRNA vaccination of SARS-CoV-2 naïve patients at 4 months post vaccination. The concentrations of antibodies to spike receptor binding domain fell over time, but the ones of some chemokine antibodies during acute state increased over 1 year. The long-term persistence of symptoms was associated with specific patterns of chemokine antibodies at 6 months. Furthermore, the specific patterns of autoantibodies against the chemokines differentiated the different COVID-19 trajectories, as well as identified other autoimmune disorders and infections. Due to the nature of chemokine function by promoting inflammation and tissue remodelling, it was suggested that the autoantibodies seem to reduce the damage caused by the inflammatory response[5].

The high concentrations of chemokine antibodies can distort the cellular migration, but the variety and levels may modulate the inflammatory response in a non-destructive manner, which then impacts the severity and clinical presentation of long COVID. Autoantibodies have an antagonising the activation of chemokines and so retention of T and B lymphocytes. Researchers are encouraged to study the chemokine-targeting agents to assess their impact on early inflammation and the development of the disease[5]. If there was a drug developed that could target the chemokine system, it could reduce the chances of developing long COVID, providing a potential approach to treatment of the disease.

UK and COVID-19

In the UK, the NIHR has invested more than 50 million to aid the understanding, diagnosis, treatment, and recovery from SARS-CoV-2. Their website reports the findings to evaluate novel approaches studied in clinical trials to ensure maximum safety and effectiveness of treatment. This information is relayed to the General Medical Council which sets the standards of good medical practice, hence best treatment method based on best available evidence[6]. There are 19 funded studies, and their feedback aids in the development of a personalised rehabilitation programme to help people recover from long COVID. The information is fully accessible to the public and allows for a newsletter sign up meaning that everyone can explore the supportive interventions the governments are putting in place to combat COVID-19[2].

Treatment and guided research

The treatment of COVID-19 remains widely symptom-based; however, new pathobiology studies offer promising explanations for condition's mechanisms and so proposes novel initiatives. The understanding of long COVID remains incomplete, although antigen persistence, dysregulation of immune response, reactivating latent viral infections, damaging microvasculature, gut dysbiosis, and many more, give valuable clues for targeted management. Long COVID can be prevented by safe and effective mRNA technology vaccines. For example, glucocorticoid receptors inhibit inflammatory cytokine, chemokine, and prostaglandin expression, hence regulating the immune balance. Drugs like oral dexamethasone and

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prednisolone contribute to lower hospitalisation rates and less persistent symptoms at 8-month follow up. Anti-inflammatory agents such as JAK inhibitors, IL-6, and TNF- blockers displayed improvement in acute COVID manifestations[3].

Treatments for myalgic encephalomyelitis/chronic fatigue syndrome (condition overlapping with long COVID), such as low dosage of naltrexone (LDN) and aripiprazole are not only anti-inflammatory but also immunomodulatory, making a safe, orally active, and low-cost alternative for long COVID therapeutic trials. LDN suppresses microglia cells of the central nervous system and weakens proinflammatory cytokines and in turn reduces hypoactivity. Since there is insufficient data to suggest definite improvement, double-blinded placebo-controlled study with 160 participants is planned, estimated to complete in April 2024. Aripiprazole is an antipsychotic agent with pleiotropic properties; anti-inflammatory and immune-modulatory through reduction in activation of microglial cells and modulation of immune-related genes. Patients report an improvement in symptoms; however, further research is needed to establish efficacy, tolerability, and safety of the drug[3].

SARS-CoV-19 infection has also been linked to changes in gut microbiome, particularly increased inflammation. In this dysbiosis, the *Ruminococcus* and *Bacteroides* concentrations rise, and *Faecalibacterium* fall, and generas such as Prevotella and Veillonella were linked to increased inflammation. In a study focusing on plant-based fiber or fermented foods in healthy adults, it has been found that high fermented diet enhances microbial diversity and decreases cytokine, chemokine, and other inflammatory serum proteins (IL-6, IL-10, and IL-12b) This suggests that this type of diet can prove to be a powerful, non-invasive modulator of the human gut microbiome and immune system axis, introducing an alternative to treating long COVID symptoms, however, further analysis is needed[3].

Those research focus strategies are being undertaken to offer tailored long COVID management and offer a blueprint for pathways yet to be discovered. Even though the vast majority is decently understood, more studies and well-designed clinical trials are needed for evidence-based approach to tackle this major global healthcare strain[3] (Bonilla et al., 2023).

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DOI: https://doi.org/10.57898/biosci.56