Post COVID and Apheresis – Where are we Standing?

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ABSTRACT

A continual increase in cases of Long/Post COVID constitutes a medical and socioeconomic challenge to health systems around the globe. While the true extent of this problem cannot yet be fully evaluated, recent data suggest that up to 20 % of people with confirmed SARS-CoV-2 suffer from clinically relevant symptoms of Long/Post COVID several weeks to months after the acute phase. The clinical presentation is highly variable with the main symptoms being chronic fatigue, dyspnea, and cognitive symptoms. Extracorporeal apheresis has been suggested to alleviate symptoms of Post/COVID. Thus, numerous patients are currently treated with apheresis. However, at present there is no data from randomized controlled trials available to confirm the efficacy. Therefore, physicians rely on the experience of practitioners and centers performing this treatment. Here, we summarize clinical experience on extracorporeal apheresis in patients with Post/COVID from centers across Germany.

Introduction

Long COVID has been defined by the British health authority (National Institute for Health and Care Excellence (NICE) as signs and symptoms that develop during or after infection with COVID-19 and last longer than 4 weeks and cannot be explained by any other diagnosis. If symptoms remain for more than 12 weeks, they are defined as Post COVID [1]. Symptoms include persistent fatigue, diffuse myalgia, depressive symptoms, non-restorative sleep, imbalance of the immune, hematological, pulmonary, cardiovascular, gastrointestinal, hepatic, renal, skeletomuscular and nervous

systems, as well as depression and anxiety [2]. The exact molecular mechanisms behind these symptoms are not understood yet but most likely heterogeneous (▶ **Fig. 1**). They might include direct or indirect consequences of the infection with SARS-CoV-2 [3]. Autoimmunity due to targeting of self-antigens due to impairment in the regulatory T cell response or molecular mimicry may be another explanation. An additional proposed mechanism for persisting symptoms is reactivation of latent viruses in the body [4]. Also, rheological abnormalities, such as blood viscosity and red blood cell (RBC) deformations were shown to be caused by COVID-19 infection [5, 6] (Toepfner et al., under review). As reviewed in [4], these different processes are not mutually exclusive and could exist in combination.

As symptoms of Long/Post COVID and adrenal insufficiency are partly overlapping this issue should be taken into account [7]. It was shown that the adrenal gland is a target of SARS-CoV-2, which potentially may directly or indirectly lead to adrenal insufficiency [8, 9]. In addition, adrenal insufficiency may be caused by glucocorticoid treatment over an extended period if then suddenly abrubted.

We have previously suggested using extracorporeal apheresis for treatment of Post COVID (at least 12 weeks after positive PCR) [10]. This treatment has received a lot of attention. However, to date, there are still no controlled randomized trials and it is still discussed whether this method is valid for treatment of people suffering from long-term symptoms after an infection with SARS-CoV-2 [11, 12]. In the current paper, we will discuss which experiments were performed to date and relate to our own clinical experience.

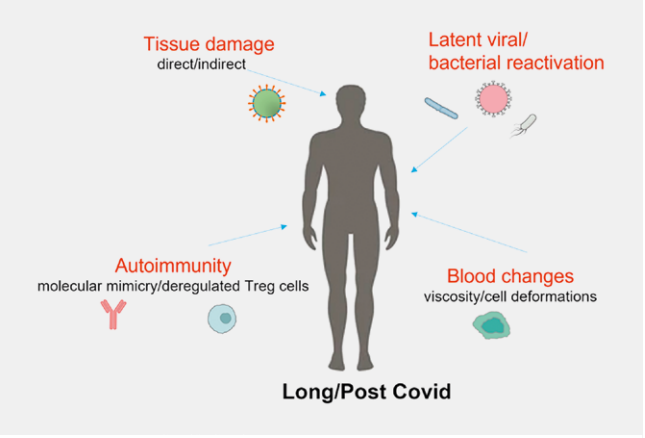
Post-infection chronic fatigue syndrome

Fatigue or muscle weakness are the most commonly reported persistent symptoms in Long/Post COVID, affecting about half of the patients for at least six months after the acute disease [2]. Long/Post COVID is not linked to the severity of the acute phase of the disease and often it appears even after mild or moderate initial illness. It is more often identified in women [13, 14]. The symptoms are similar to those seen in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) or those observed after the Russian or Spanish flu [15, 16]. The pathology of ME/CFS is not known, but probably it results from the dysregulation of multiple systems in response to a particular trigger.

Due to its resemblance with Long/Post COVID, a common etiopathogenesis has been suggested [17, 18]. Unexplainable post-acute infection syndrome (PAIS) is not unique to SARS-CoV-2 infections, but has been reported for all kinds of infectious agents, including bacteria, viruses, and parasites For example, PAIS has been reported for a number of viruses, such as Epstein-Barr (EBV), Ebola, Dengue, polio, SARS-CoV-1, Chikungunya, West Nile, Ross River, and enteroviruses [4]. Non-viral pathogens known to trigger PAIS are *Coxiella burnetti*, *Borrelia*, and *Giardia lamblia* [4]. Due to missing knowledge about the underlying mechanisms, there is often a poor recognition of these conditions in clinical practice.

Molecular mimicry and autoantibodies

Underlying pathological mechanisms of ME/CFS are largely unknown, but the presence of autoantibodies, cytokine pattern deviations and the presentation of cognitive and autonomic nervous



▶ **Fig. 1** Potential explanations for fatigue symptoms in Long/Post COVID.

system related symptoms provide evidence for ME/CFS being an immunological disorder with elements of autoimmunity triggered by the preceding infection [19] . Certain pathogens have the ability to escape from host immune response. Due to host protein mimicry no antibodies against the pathogen is created [20]. Oppositely, similarity between pathogenic antigens and host proteins may lead to immune cross reactivity, whereby the reaction of the immune system towards the pathogenic antigens may harm similar human proteins, essentially causing autoimmune disease [21]. Increased levels of autoantibodies binding to G-protein coupled receptors (GPCRs), such as adrenergic and muscarinic receptors, were found in ~30 % of ME/CFS-patients [22]. Furthermore, autoantibodies against neuronal proteins, such as serotonin receptors, glial fibrillary antigen (GFAP) and S100, have been observed [23]. In Norway, clinical trials showed that in a subgroup of ME/CFS patients, prolonged B-cell depletion with rituximab maintenance infusions was associated with sustained clinical response [24, 25] although later there were problems confirming these results [26].

A number of studies have suggested that molecular mimicry may also play an important role in autoimmunity generation in COVID-19 [27, 28]. For example, hexapeptides of the SARS-CoV-2 spike glycoprotein (S) and nucleocapsid protein (N) show notable similarity with three human proteins, DAB1, AIFM, and SURF1, involved in neuron development and mitochondrial metabolism [29]. Cross-reactivity of several other SARS-CoV-2 amino acid sequences with human proteins including proteins on the plasma membrane of olfactory neurons and endothelial cells, and in the cytoplasm of B cells and macrophages have also been detected [27].

Indeed, autoantibodies against various epitopes have been detected in patients with Long/Post COVID, suggesting that chronic fatigue in these patients may be caused by autoimmune mechanisms. More studies showed that antibodies against type I interferons (IFNs) were present in ~10 % of patients with a severe COVID-19 course and correlated with increased CRP and lower lymphocyte counts [30–32]. Such autoantibodies neutralize the ability of the corresponding type I IFNs to block SARS-CoV-2 infection explaining why these antibodies are not observed in asymptomatic patients or those with a mild course [30].

As in ME/CFS, antibodies against GPCRs were also observed in Long/Post COVID patients [33, 34]. In a study with 31 patients suffering from different Long/Post COVID symptoms after recovery from the acute phase of the disease, autoantibodies against these receptors were found in all patients [34]. This explains why the aptamer BC007 for neutralization of autoantibodies against GPCRs has been suggested for treatment of Post COVID symptoms and currently BC007 has been used in individual patients with Post COVID.

Until now, no correlation between GPCR autoantibody levels and disease severity could be observed [35]. Therefore, the role of increased β adrenergic and muscarinic cholinergic receptor autoantibodies in the pathogenesis of ME/CFS and Long/Post COVID is still uncertain and further research is needed to evaluate the clinical significance of these findings.

Viral/bacterial reactivation due to COVID-19

Reactivation of cytomegalovirus (CMV) and other herpesviridae, such as EBV and HHV6, in critically ill patients is common and associated with an increased risk of secondary infections and mortality [36–39]. Similar observations have been noticed for COVID-19 patients, where direct pathogenic effects, an unregulated host response and the use of strong immunosuppressants (tocilizumab) or high doses of steroids may induce immunosuppression.

In a study from Italy with 431 COVID-19 patients admitted to the intensive care unit (ICU), CMV blood reactivation was observed in ~20 % of the patients [40]. The severity and the occurrence of secondary bacterial infections were associated with an increased risk for this CMV reactivation. On the other hand, the CMV reactivation did not affect the outcome of the patients [40]. Conversely, a study from China showed that ~25 % of COVID-19 patients had EBV reactivation. The EBV reactivation was associated with age and female gender and a tendency of a higher mortality rate [41]. As compared to patients with COVID-19 who did not receive anti-EBV therapy with ganciclovir, ganciclovir-treated patients reportedly had improved survival rate [41].

In another pilot observational study from Ukraine, 88 COVID-19 patients were recruited, including 68 subjects with reactivation of herpes viruses and 20 subjects without detectable DNA of herpesviruses. Patients with Long/Post COVID manifestations presented with reactivation of EBV in 42.6 %, HHV6 in 25.0 %, and EBV plus HHV6 in 32.4 % of the cases. Compared with controls, patients with herpes virus infections presented with significantly more symptoms of Long/Post COVID, elevated CRP and D-dimer, and suppressed cellular immune response [42]. These results indicate a potential involvement of reactivated herpes virus infections, in severe COVID-19 and formation of Long/Post COVID. Reactivation of hepatitis B virus (HBV) in COVID-19 patients has also been observed in a smaller number of cases [43, 44].

About one-third of the world's population is thought to be infected with latent *Mycobacterium tuberculosis*. Both previous and newly developed tuberculosis (TB) infections are risk factors for COVID-19 and are associated with poor outcomes. Clinical evidence suggests that SARS-CoV-2 infection may predispose patients to TB infection or may lead to reactivation of latent disease. Similarly, underlying TB disease has been reported to worsen COVID-19 [45].

A chronic stimulation of the immune system due to a persistent infection, as observed in other diseases, has not been observed for SARS-CoV-2 to date [46] but cannot be ruled out. In order to further elucidate the role of persisting infections with SARS-CoV-2 and other viruses, we recommend a large-scale investigation of possible benefits of screening and treatment of chronic infections in COVID-19 patients for prevention of Long/Post COVID.

Other mechanisms responsible for Long/Post COVID

In addition to the potential mechanisms leading to Long/Post COVID mentioned above, COVID-19 can increase blood viscosity through modulation of fibrinogen, albumin, lipoproteins, and RBC indices. This may decrease tissue oxygenation, which can cause cardiovascular and neurological complications in COVID-19. Increased blood viscosity with or without abnormal RBC function in COVID-19 may impair tissue oxygenation and thereby foster the development of cardio-metabolic complications and Long/Post COVID [47].

Oxidative stress is defined as an imbalance between elevated levels of cellular reactive oxygen species (ROS) and low activity and/or levels of antioxidant defenses [48]. ROS production is an important mechanism for resolving infections, however, excessive ROS production can result in tissue damage leading to endothelial dysfunction, increased inflammation, compromised lymphocyte function, and disrupted neurotransmitter assembly [49–51]. Specifically, oxidative stress can lead to mutations in mitochondrial DNA, injury to the mitochondrial respiratory chain, activation of the defense systems in mitochondria and alterations in the membrane permeability [52]. Additionally, oxygen supplementation used to treat patients with severe COVID-19 can lead to increased ROS generation in the mitochondria. This damages mitochondrial complexes and decreases oxidative phosphorylation leading to reduced production of ATP and elevation in apoptosis rate. Damage of mitochondria by hyperoxia may reduce antiviral reactions and result in increased tissue damage [52]. Recently, excessive inflammation and oxidative stress have been considered as main factors leading to fibrosis, thrombosis, autonomic nervous system dysfunction and autoimmunity, which together result in tissue damage and thus Long/Post COVID [51, 53].

Furthermore, in the context of Long/Post COVID, psychological factors need to be considered. For example, based on data obtained from a large cohort, a French study suggested that persistent physical symptoms following COVID-19 infection might be associated more with the belief in having been infected with SARS-CoV-2 than with having laboratory-confirmed COVID-19 infection, which further emphasizes the heterogeneity of this patient population and the need of a multidisciplinary approach towards diagnostics and treatment [54]. Therefore, non-specific mechanisms unrelated to SARS-CoV-2 virus infection should also be taken into account [55].

Apheresis for treatment of Post COVID

As mentioned above, a number of agents have been proposed to contribute to Long/Post COVID. Apheresis has been suggested as a way to treat patients suffering from Post COVID (at least 12 weeks after acute COVID-19). Apheresis is an extracorporeal method for removal of selected blood components, either specific cells or specific components of the plasma. The methods for removal of different pathogenic molecules from plasma were initially developed

for removal of lipids for treatment of severe dyslipidemias and for removal of autoantibodies. There are several types of apheresis mainly based on three physical mechanisms: filtration, precipitation and adsorption, whereby lipids, immunoglobulins, inflammatory agents and further molecules are removed from the blood. Apheresis can be roughly divided into whole blood and plasma based methods, in which the cell-rich fraction must first be separated from the plasma. Whole blood methods are based on the principle of adsorption on either polyacrylate-coated beads (DALI) or dextran sulfate (Liposorber D). In plasma methods, protein lowering relies on different principles, such as filtration by size (MONET, Lipidfiltration, INUSpheresis, and FractioPlas, precipitation of lipoproteins after pH lowering and the addition of an excess of heparin (H.E.L.P.), adsorption by antibodies against, for example, apolipoprotein B (TheraSorb) or against Fc-fragments for removal of autoantibodies [56–59]. While these methods were initially developed for removal of lipids in severe dyslipidemias, subsequent studies showed that they have multiple additional beneficial effects due to removal of high molecular weight proteins and improving blood viscosity, removal of oxLDL and reducing oxidative stress, removal of cytokines and finally removal of autoantibodies [60–63]. A recent proteomic analysis showed that lipoprotein apheresis also removed other proinflammatory and proatherogenic factors [64]. Depending on the filters used (INUS 30, INUS 50 and TKM58), a reduction and removal of proatherogenic proteins in different quantities was achieved. This included not only apolipoproteins, CRP, fibrinogen, and plasminogen (INUS 30, INUS 50) but also proteins, such as complement factor B (CFAB), protein AMBP, afamin, and the low affinity immunoglobulin gamma Fc region receptor III-A (FcγRIIIa) (TKM58) [64].

The rationale for using apheresis to treat Post COVID was recently addressed in a statement by the German Society of Nephrology (https://www.dgfn.eu/stellungnahmen-details/stellungnahme-der-deutschen-gesellschaft-fuer-nephrologie-zu-lipidapherese-bei-long-oder-post-covid.html, accessed on the 25th of June 2022). While the German Society of Nephrology saw no justification for lipid removal in Post COVID, it was concluded that there is a rationale for autoantibody removal, for example, by immunoadsorption, and therefore clinical studies to investigate the efficiency of this therapeutic approach are urgently needed [15, 16].

Currently, numerous patients with ME/CFS symptoms due to Post COVID are treated with apheresis. However, until now, no controlled randomized trials have been performed and there are no publications on this subject. Nevertheless, several centers in Germany have started performing apheresis therapy using size filtration, H.E.L.P., or immunoadsorption approaches with variable results. In some Post COVID patients, short-term improvements were observed but often for just a few weeks. Because of different filters used at different centers and no defined patient groups, it is usually impossible to compare results. Thus, these observations suggest that apheresis may have benefits in certain patients but in many other patients, apheresis alone may not be sufficient. Therefore, it has been proposed that apheresis should be combined with steroid treatment in order to decrease the amount of autoantibodies produced. This is in accordance with our knowledge about other antibody-mediated neurological diseases, for example, multiple sclerosis or chronic inflammatory demyelinating polyneuropathy, where apheresis therapy alone cannot be successful, but needs accompanying immunosuppressive/immunomodulatory therapy to inhibit further production of the pathogenic compounds. Therefore, in the above-mentioned diseases, drug therapy is always the primary option and apheresis therapy is used only in acute deterioration [65].

In Cham in Germany, a cohort of patients with ME/CFS was treated with a filtration-based therapeutic apheresis approach, specifically INUSpheresis, which is known to remove autoantibodies, inflammatory cytokines, oxidated LDLs, environmental toxins and large molecules, contributing to plasma viscosity. In order to prevent further production of autoantibodies after their removal, the treatment protocol included application of prednisolone between the apheresis treatment sessions. To increase the antioxidant and anti-inflammatory effects, the protocol also included high doses of vitamin C. Included were 1111 patients (2009–2022) with ME/CFS (148 following COVID-19, 963 other infections (e. g., Lyme disease, toxoplasmosis, EBV, or chlamydia), environmental factors (e. g., organic solvents) or unknown cause). However, no placebo controls were included. Following this protocol, 56 % of the patients reported to be without symptoms or substantially improved following 2nd INUSpheresis (TKM58), 64 % were without symptoms or substantially better following 3rd INUSpheresis (TKM58 or INUS 30) and additional therapy (prednisolone or vitamin C), and 74 % were without symptoms or significantly better 6 months after INUSpheresis with follow-up therapy. Eleven percent of the ME/CFS patients experienced a moderate improvement and 15 % did not encounter an improvement. The promising results of this empirical treatment with INUSpheresis in a heterogeneous population of patients with ME/CFS emphasize the need for a placebo-controlled study using therapeutic apheresis methods in Post COVID patients in order to generate scientific evidence to justify introduction of this treatment approach into clinical practice.

Conclusion

Despite promising experiences with several forms of apheresis in the treatment of Post COVID, either alone or in combination with other therapies, confirmatory data on its efficacy from large well-designed interventional studies is still lacking. A randomized sham-controlled trial is therefore needed and should include a defined patient group with Post COVID (at least 12 weeks after positive PCR) with fatigue and other symptoms. Optimally, this should be a 3-arm trial, where the patients should be randomized for filtration, immunoadsorption, or a sham procedure. All patients should undergo structured evaluation of fatigue severity using a questionnaire and a visual analogue scale of tiredness, as well as a detailed clinical evaluation of the other symptoms before and after the treatment. Also, blood samples should be collected before and after the treatment in order to measure blood count, routine biochemical parameters, rheological parameters, markers of oxidative stress, immunoglobulins A, M and G, autoantibodies against α and β adrenergic, muscarinic cholinergic receptors, ACE2, MASR, AT1R, ETAR, ETBR, PAR1, bradykinin receptor and CXCR3 in the plasma and Real-Time-Deformability-Cytometry of patients' blood should optimally be performed.

Based on previous research, it might be postulated that in patients with Post COVID, extracorporeal apheresis may lead to a significant reduction of autoantibodies while maintaining an adequate immune response against SARS-CoV-2 and other pathogens. Moreover, this quantitative decrease in autoantibodies might translate into alleviation of Post COVID related symptoms and clinical outcomes.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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