Thieme

A Single-Center Pilot Study of Therapeutic Apheresis in Patients with Severe Post-COVID Syndrome

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ABSTRACT

After the COVID-19 pandemic, many patients have reported chronic fatigue and severe post-exertional malaise, with symptoms similar to those of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). The accumulation of agonistic receptor autoantibodies targeting beta-adrenergic (β1 and β2) and muscarinic (M3 and M4) neurotransmitter receptors may play a crucial role in the pathomechanism of both ME/CFS and post-COVID conditions. Therapeutic apheresis has been suggested as an effective treatment option for alleviating and mitigating symptoms in this desperate group of patients. In this single-center pilot study, we analyzed autoantibodies in a cohort of 20 post-COVID patients before and after therapeutic apheresis. Apheresis resulted in a decline of β1 or β2 adrenergic receptor antibodies in all patients. Additionally, the majority of patients experienced a concurrent reduction in symptoms such as fatigue, physical activity restrictions, myalgia, post-exertional malaise, and concentration disorders. This study clearly demonstrates an association between autoantibodies and the clinical improvement of post-COVID patients. Even if future sham-controlled trials do not show a positive outcome, extracorporeal apheresis may still be valuable for this patient group by temporarily improving microperfusion and symptoms. Success in restoring patients to work and normal life, as observed in many individuals after therapeutic apheresis, should be recognized. Therefore, we believe that extracorporeal therapeutic apheresis, as part of a multimodal treatment, should be considered an early intervention for postinfectious syndromes in selected patients.

Introduction

The chronic fatigue syndrome (CFS) or myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is an illness of uncertain etiology. The pathophysiology is currently not clear, and there are no specific diagnostic tests with sufficient sensitivity and specificity [1]. Recent studies have investigated antibodies targeting neurotransmitter receptors in a subset of patients with infection-triggered diseases [2]. Current studies highlight several connections between the pathology of ME-CFS and the post-COVID syndrome [3–5]. The post-COVID syndrome affects up to 20 % of patients following recovery from acute SARS-CoV-2 infection [6, 7]. It can manifest with various symptoms, including fatigue, cognitive impairment, sleep disturbances, and shortness of breath [8]. The accumulation of agonistic receptor autoantibodies (AAbs) targeting beta-adrenergic (β1 and β2) and muscarinic (M3 and M4) neurotransmitter receptors may play a crucial role in the pathomechanism

of both ME/CFS and post-COVID [9, 10]. In addition, several patient-level risk factors have been shown to increase the risk of post-COVID. According to a recent meta-analysis, among COVID-19 survivors, older age, female sex, higher Body Mass Index (BMI), smoking, the presence of physical and mental comorbidities, and hospitalization or admission to the ICU are associated with a higher risk of post-COVID [11]. Some studies have observed a beneficial effect of immunoadsorption treatment in patients testing positive for AAbs [2]. Due to the limited treatment options available, patients often seek specialized centers for apheresis treatment. The current study retrospectively analyzed the effect of apheresis treatment in 20 patients with a high likelihood of infection-triggered post-COVID syndrome. The patients underwent therapeutic apheresis with immunoglobulin reduction, comparable to immunoadsorption therapy as described earlier [12]. The treatment was administered five times at weekly intervals. The severity of symptoms was assessed using modified disease-specific scores based on a modified questionnaire developed by Fluge et al. [13]. Additionally, agonistic receptor AAbs were measured.

Subjects and Methods

Patients and assessment of post-Covid symptoms

In Bochum, Germany, a cohort of 20 patients who had previously tested positive for SARS-CoV-2 in a PCR test and were diagnosed with post-COVID syndrome and chronic fatigue syndrome underwent therapeutic apheresis. Prior to treatment initiation, patients were thoroughly examined to exclude other potential causes of chronic fatigue syndrome. Symptom evaluation was conducted using standardized questionnaires for post-COVID, including symptoms outlined in the Canadian Consensus Criteria for ME/CFS [14]. A modified questionnaire developed by Fluge et al. [13] was utilized to assess symptoms before the first and after the final apheresis treatment. Symptoms were categorized on a scale ranging from 0 to 9, with 0 indicating no symptoms, 5 indicating moderate symptoms, and 9 indicating very severe symptoms. Included patients had a score of ≥ 6 in at least 4 out of the 5 criteria (tiredness, restriction of physical activity, myalgia, post-exertional malaise, concentration disorders). In accordance with the ethical guidelines during the pandemic, all participants in the study have provided written consent, and all samples have been analyzed completely anonymously.

Therapeutic apheresis (toxopheresis)

A group of 20 patients diagnosed with severe post-COVID syndrome underwent therapeutic apheresis, specifically toxopheresis, which is a filtration-based technique using SelectiSmart M plasma filters. This method is effective in removing AAbs, inflammatory cytokines, lipoproteins, and large molecules that contribute to plasma viscosity [15]. The patients received a total of five treatments, administered once per week for five weeks. Each treatment involved a tagged plasma volume of four liters, and patients received 5000 IU of heparin prior to apheresis.

Adrenergic receptor antibodies

Blood samples were collected from patients both before the initial treatment and after the final treatment. The analysis specifically targeted antibodies against β1 and β2 adrenergic receptors, and in 8 patients, additional testing was conducted for antibodies against muscarinic acetylcholine receptors 3 and 4. These analyses were carried out at a specialized institute in Berlin, Germany (IMD Labor Berlin, Berlin, Germany), following the manufacturer's instructions for measuring the blood samples.

Results

Patients' characteristics

The cohort consisted of 13 (65 %) female and 7 (35 %) male participants. The primary symptoms reported by the participants included tiredness, restriction of physical activity, myalgia, post-exertional malaise, and concentration disorders.

Adrenergic receptor antibodies

All patients underwent testing for β1 and β2 adrenergic receptor antibodies prior to apheresis. Among the 20 patients, 6 (30 %) had elevated β1 adrenergic receptor antibodies, while 10 (50 %) had elevated β2 adrenergic receptor antibodies. Additionally, testing for M3 and M4 adrenergic receptor antibodies was conducted in 8 of the 20 patients. Among these 8 patients, 2 (25 %) had elevated M3 adrenergic receptor antibodies, while none of the 8 patients tested had elevated M4 adrenergic receptor antibodies (▶ **Table 1**).

The levels of β1 adrenergic receptor antibodies were significantly reduced after the final apheresis treatment (14.9 ± 17.8 vs. 7.3 ± 9.2; p = 0.0002; ▶ **Fig. 1a**). On average, there was a 40.8 ± 28.0 % reduction in β1 adrenergic receptor antibodies compared to baseline (▶ **Fig. 1b**). In two patients with initially high values, β1 adrenergic receptor antibodies were reduced but remained above the reference value after apheresis. In one patient, β1 adrenergic receptor antibodies increased by 32 %, although they were not detected before apheresis and remained below the reference value (pre: below 2.5 U/ml/post: 3.3 U/ml). Similarly, β2 adrenergic receptor antibodies were significantly reduced after the last apheresis treatment (15.6 ± 19.9 vs. 6.9 ± 11.2; p = 0.0003; ▶ **Fig. 1c**). The mean reduction in β2 adrenergic receptor antibodies compared to baseline was 45.2 ± 27.0 % (▶ **Fig. 1d**). In three patients, β2 adrenergic receptor antibodies were reduced but remained above the upper reference value after apheresis. Regarding M3 adrenergic receptor antibodies, there was a significant reduction after the last apheresis treatment (7.1 ± 3.6 vs. 3.2 ± 0.9; p = 0.0156; ▶ **Fig. 2a**). The mean reduction in M3 adrenergic receptor antibodies compared to baseline was 47.4 ± 21.4 % (▶ **Fig. 2b**). For M4 adrenergic receptor antibodies, there was also a significant reduction after the last apheresis treatment (6.3 ± 3.3 vs. 3.4 ± 0.9; p = 0.0142; ▶ **Fig. 2c**). The mean reduction in M4 adrenergic receptor antibodies compared to baseline was 39.5 ± 16.9 % (▶ **Fig. 2d**).

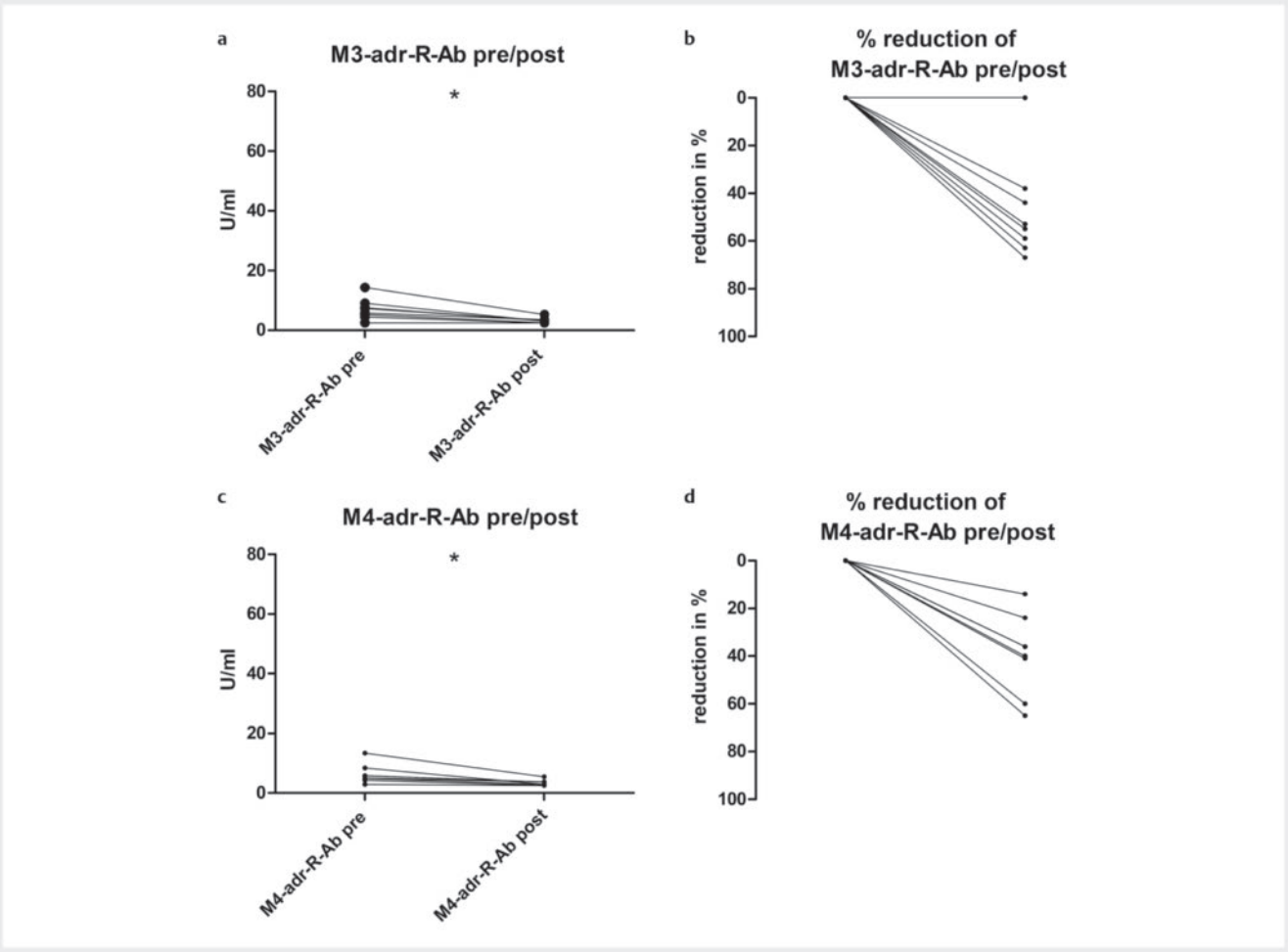
Clinical Course

At the beginning of the study, all patients experienced tiredness, post-exertional malaise, concentration disorders, myalgia, and restriction of physical activity. The changes in symptoms pre and post

▶ **Table 1** Concentration of adrenergic receptor antibodies before and after apheresis.

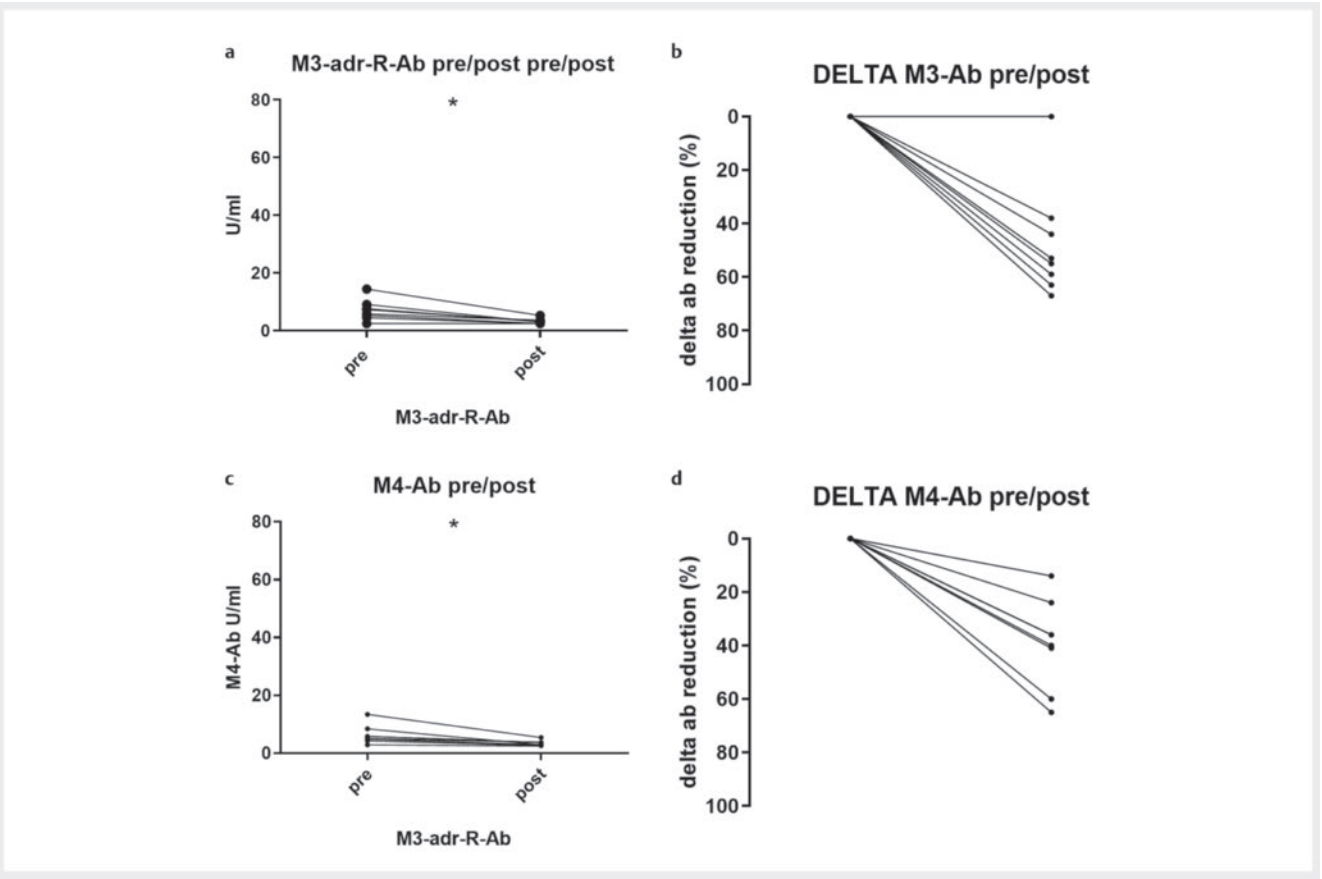
	β1-adr-R-Ab (U/ml)	B2-adr-R-Ab (U/ml)	M3-adr-R-Ab (U/ml)	M4-adr-R-Ab (U/ml)
Before apheresis	14.9 ± 17.8	15.6 ± 19.9	7.1 ± 3.6	6.3 ± 3.3
After apheresis	7.3 ± 9.2	6.9 ± 11.2	3.2 ± 0.9	3.4 ± 0.9
Mean reduction in %	40.8 ± 28.0	45.2 ± 27.0	47.4 ± 21.4	39.5 ± 16.9
Upper reference value	15	8	8	10.7
Patients above reference (n)	6/20 (30 %)	10/20 (50 %)	2/8 (25 %)	0/8 (0 %)

adr-R-Ab: Adrenergic receptor antibodies; n: Number.



▶ **Fig. 1** Therapeutic apheresis reduces the amount of β adrenergic autoantibodies: **a**: Levels of β1 adrenergic receptor antibodies before (pre) and after (post) therapeutic apheresis treatment; **b**: Percentage reduction of β1 adrenergic receptor antibodies before (pre) and after (post); **c**: Levels of β2 adrenergic receptor antibodies before (pre) and after (post) therapeutic apheresis treatment; **d**: Percentage reduction of β2 adrenergic receptor antibodies before (pre) and after (post). Note: adr-R-Ab refers to adrenergic receptor antibodies.

apheresis are presented in ▶ **Fig. 3**. Following apheresis, 12 out of 20 (60 %) patients reported improvement in tiredness, while 6 (30 %) reported no change and 2 (10 %) reported worse tiredness. Improvement in restriction of physical activity was reported by 17 out of 20 (85 %) patients, with 3 (15 %) reporting no change and none reporting worse restriction of physical activity. Myalgia showed improvement in 15 out of 20 (75 %) patients, with 4 (20 %) reporting no change and 1 (5 %) patient not responding to the question. Post-exertional malaise improved in 15 out of 20 (75 %) patients, with 4 (20 %) reporting no change and 1 (5 %) patient reporting worse post-exertional malaise. Concentration disorders im-

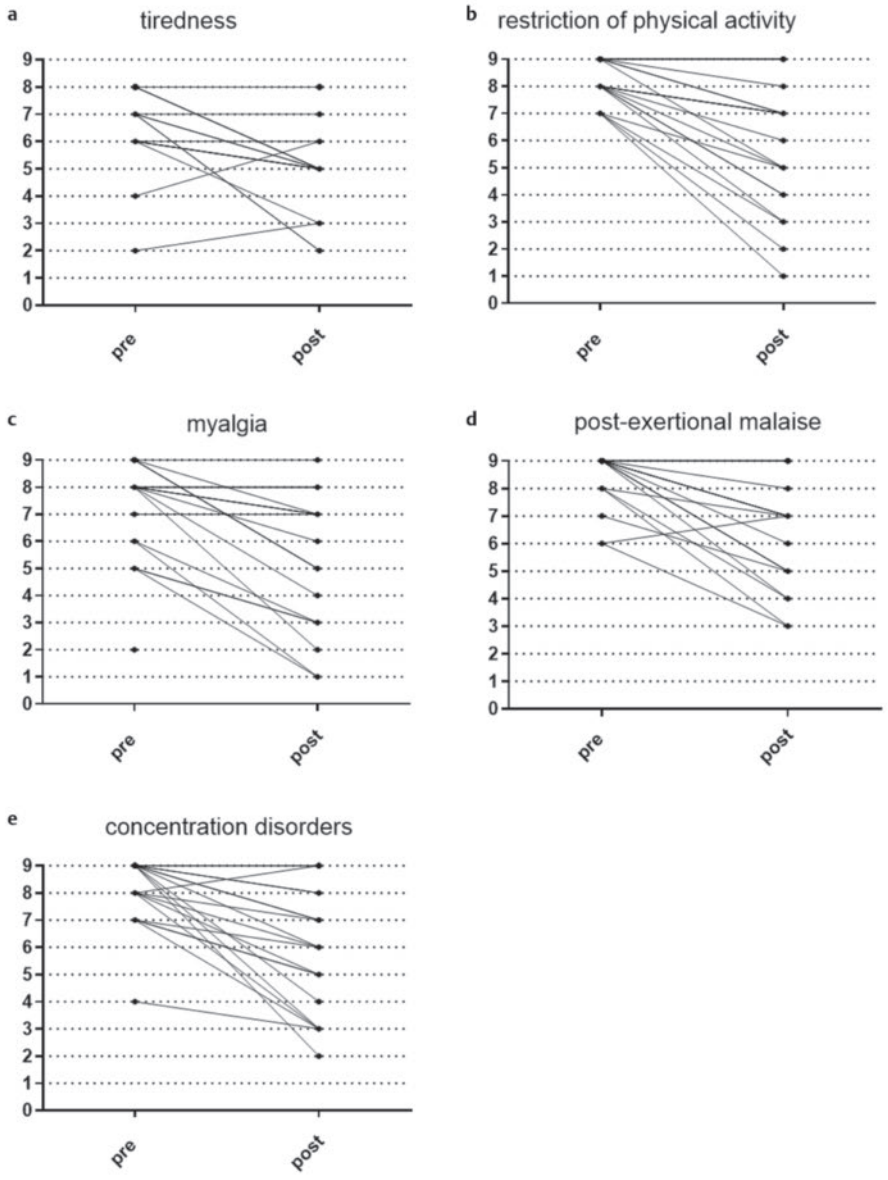


▶ **Fig. 2** Therapeutic apheresis reduces the amount of β adrenergic autoantibodies: **a**: Levels of M3 adrenergic receptor antibodies before (pre) and after (post) therapeutic apheresis treatment; **b**: Percentage reduction of M3 adrenergic receptor antibodies before (pre) and after (post); **c**: Levels of M4 adrenergic receptor antibodies before (pre) and after (post) therapeutic apheresis treatment; **d**: Percentage reduction of M4 adrenergic receptor antibodies before (pre) and after (post). Note: adr-R-Ab refers to adrenergic receptor antibodies.

proved in 17 out of 20 (85 %) patients, with 2 (10 %) reporting no change and 1 (5 %) patient reporting concentration disorders after apheresis.

Discussion

This single-center study describes the course of 20 patients with post-COVID after apheresis therapy. Apheresis resulted in a decline in β1 or β2 adrenergic receptor antibodies in all patients. Moreover, the majority of patients experienced a concurrent reduction in symptoms such as tiredness, restriction of physical activity, myalgia, post-exertional malaise, and concentration disorders. However, none of the patients achieved a complete reduction in the symptom scores reported in the questionnaire following apheresis. In recent research, it has been observed that the clinical fatigue improved following the therapeutic elimination of adrenergic receptor antibodies in individuals with ME/CFS and post-COVID [10, 15, 16]. The correlation between post-COVID symptoms and adrenergic receptor antibodies is further supported by the findings from our study. However, not all patients appear to respond equally to antibody reduction. Giszas et al. described the course of two patients with post-COVID following apheresis and successful antibody elimination. One patient benefited significantly, while the second patient continued to experience persistent symptoms. Both patients experienced a subsequent rise in antibodies after apheresis, which the authors attributed to a strong autoimmune component of the post-COVID disease [16]. In our findings, we observed varying efficacy in the removal of adrenergic receptor antibodies through apheresis. This implies the need for individualized therapeutic apheresis protocols, ensuring that the levels of relevant adrenergic receptor antibodies are consistently below their respective threshold values. It is important to note that therapeutic apheresis leads to a reduction in antibodies comparable to immunoadsorption, as used in the studies conducted by Tölle et al. [17] and Stein et al. [18, 19], which also resulted in a temporary reduction of symptoms in a subgroup of patients with post-COVID ME/CFS. This observation was also supported by an analysis of 27 patients with post-COVID and elevated antibodies [15]. Considering the potential for a rebound response, adjustments to the therapeutic regimen, such as incorporating immunosuppressant therapy, may be necessary to minimize this risk [9]. Besides antibodies, numerous other biomarkers may be associated with post-COVID, including markers of systemic inflammation, acute phase proteins, cytokines, and chemokines [20, 21]. A meta-analysis by Yin et al. revealed that elevated interleukin (IL)-6 levels were correlated with post-COVID [22]. Reduction of inflammatory cytokines could potentially alleviate symp-



▶ **Fig. 3** Symptoms are reduced after therapeutic apheresis: **a**: Patients' symptoms before and after apheresis. Symptom scores for tiredness (**3a**), restriction of physical activity (**3b**), myalgia (**3c**), post-exertional malaise (**3 d**), and concentration disorders (**3e**) are indicated on a scale from 0 (absent) to 9 (most severe).

toms in post-COVID patients post-apheresis, as double filtration apheresis has demonstrated the ability to decrease levels of various cytokines and chemokines, such as IL-8, macrophage inflammatory protein (MIP)-1α, IL-5, IL-4, and interferon (IFN)-γ [23].

Limitations of the study include its single-center design and the absence of a control group. It is not feasible to implement a sham apheresis in this particular setting. Additionally, the potential placebo effect should not be disregarded as we cannot exclude a strong psychological effect of the intervention in these patients that may be unrelated to inflammation and autoimmunity. The placebo effect in clinical trials can present advantages by providing a baseline for evaluating treatment outcomes and studying the psychosocial aspects of healing. However, it poses limitations as it may confound the assessment of true treatment efficacy and create challenges in designing placebo-controlled studies. Understanding the maximum extent of placebo effectiveness is crucial for accurately interpreting treatment responses and ensuring evidence-based practice.

Even if future sham-controlled trials do not show a positive outcome, the ability of extracorporeal apheresis to improve microperfusion and clinical symptoms for a certain period may still hold value for this desperate group of patients. When a patient can resume work and normal life over a longer period, as we have observed in numerous individuals after therapeutic apheresis, this could be seen as a success of practice-oriented medicine [24].

Given the heterogeneity of this patient group, conducting a randomized clinical evidence-based trial will be challenging. Therefore, an individualized, practice-oriented, multimodal treatment strategy is likely to be the best approach for these patients [5].

Conflict of Interest

JK and AV are clinicians at Apherese-Zentrum am Kortumpark. MH is CEO at Medica GmbH.

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