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Treatment of Chronic Fatigue Syndrome (CFS) in Post-SARS-CoV-2 Infection through combined outpatient Neuromodulation Therapy with Repetitive Transcranial Magnetic Stimulation (rTMS) and Ketamine IV Therapy - A Case Series

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ABSTRACT

The most reported symptom of post-COVID syndrome is pronounced fatigue.[1,2] In this case series, we present the treatment of four patients suffering from Post-COVID syndrome after more than 3 months since infection, presented diagnostically within the framework of chronic fatigue syndrome (CFS). They were treated with a combination of Low-frequency (1 Hz) repetitive transcranial magnetic stimulation (rTMS) and ketamine intravenous (IV) infusion therapy for a period of 2 to 3 weeks. Three patients experienced significant improvement. Given the promising results further researchis indicated.

Keywords: Post-COVID Syndrome; SARS-CoV-2; Ketamine; rTMS; Chronic Fatigue Syndrome; Neuroplasticit

INTRODUCTION

Robert Koch Institute (RKI) and UK National Institute for Health and Care Excellence (NICE) guideline recommendation defines "Long-COVID" as physical and psychological symptoms that persist after the acute illness phase of SARS-CoV-2 infection of 4 weeks. "Post-COVID syndrome" (PCS) refers to afflictions that are still present more than 12 weeks after the onset of SARS-CoV-2 infection and cannot be explained in any other way. Anyone who has been infected with the virus that causes COVID-19 can experience post-COVID conditions, even people who had mild illness or no symptoms from COVID-19.[3]

"Post-Covid Syndrome" consists of varied and differently pronounced symptoms such as dizziness, extreme exhaustion, general weakness (fatigue), olfactory and gustatory disturbances, memory and concentration problems, sleep disturbances, non-restorative sleep, nocturnal leg movements and twitching, symptoms than worsen for more than 24 hours after exertion, muscle and joint pain without redness and swelling, headaches, tender lymph nodes on the neck/under the armpits, depressive moods, fever and visual disturbances.[4] Chronic fatigue syndrome (CFS) is particularly typical of long covid and the data available to date indicates that pronounced fatigue is the most common of post-COVID symptoms.[1,2]

Chronic fatigue also occurs in other diseases such as multiple sclerosis, cancer, fibromyalgia or after certain viral infections. CFS is also correlated to high inflammation rates in the body.[5] Treatments with repetitive transcranial magnetic stimulation (rTMS) have already been successfully carried out for some of these conditions.[6] Alternating magnetic fields acting on the head from the outside stimulate the nerve cells in the brain to electrical activity and activate them.[7] Furthermore, newer studies could show that another mechanism of action in rTMS seems to be its glial activation which leads to anti-inflammatory effects.[8]

We supplemented rTMS treatment for post-COVID syndrome in parallel with ketamine IV infusions. One major mechanism of action in Ketamine (a NMDAR antagonism) is the induction of "brain plasticity synaptic, structural, and functional changes, particularly in pyramidal neurons in the prefrontal cortex",[9] i.e., the brain's capacity to build new functional networks and recent studies support the assumption that hippocampal neurogenesis takes place.[10] RTMS is disposed to synergistically enhance the effect of ketamine therapy and may provide a more sustained improvement in the symptoms of Long Covid.[11]

The treatment of this presented case series focused on reducing the typical symptoms of CFS such as fatigue and exhaustion by promoting neuroplasticity and reducing inflammation rates through a combination treatment of ketamine IV infusions and low-frequency rTMS (LF- rTMS) over the right dorsolateral prefrontal cortex (DLPFC) area, which is particularly correlated with CFS syndrome.[12] LF-rTMS has already been successfully applied in other inflammatory diseases like Fibromyalgia Syndrome.[13] Furthermore, from our experience we can report that LF-rTMS is perceived as more comfortable and relaxing to many patients compared to high-frequency rTMS (HF- rTMS). These two considerations led to the decision to use LF-rTMS in our study design.

METHOD

The study participants were recruited via advertisements in social media and the clinic's website. Treatment was provided free of charge.

Inclusion Criteria

- Meeting the diagnostic criteria for CFS formulated by the Centers for Disease Control and Prevention (CDC).
- Age: 15 – 70 years
- At least 3 months lying in-between PCR test negative and start of study participation
- Unremarkable internal and orienting neurological examination.
- Unobtrusive laboratory values not older than 1 month before study participation: blood count, T3, T4, TSH, vitamin B12, inflammation parameters.

Exclusion Criteria

- history of major depression or other psychiatric diagnoses.
- significant impairment of lung function
- history of seizure disorders, heart failure, diabetes, MS, autoimmune diseases
- contraindications for rTMS: epilepsy, cochlear implants, brain electrodes or implants
- contraindications for ketamine: poorly controlled hypertension, untreated glaucoma, intracranial pressure symptoms, severe coronary artery disease, psychosis/schizophrenia

Measures

The following psychometric tests for pre and post measurement were used:
BDI-II (Depression Inventory), FSS (Fatigue Scale Self-Test), D2-R (Concentration and Attention Test).

Treatment Course

- 6 ketamine iv infusions 0.5mg/kg bw over 35 to 45 min.
- 20 sessions of LF-rTMS over right DLPFC with following protocol: 1 Hz at 120% MT
- Treatment location assessed through neuro-cardiac guided (NCG) rTMS
- Treatment period: 2 to 3 weeks in total.
- Therapy frequency: 2 rTMS per day, 3 ketamine infusions per week with 1 day interval.

Participants and symptomatology before the start of treatment

A total of 4 clinical cases were treated. Age: between 19 - 28 years, 2 male, 2 female patients. All 4 patients were infected with a medically confirmed SARS-CoV-2 infection and had tested negative for at least 3 subsequent months at the start of study participation.

Main symptoms

All 4 study participants described marked fatigue symptomatology at baseline: physical and mental fatigue, reduced ability to concentrate, impaired working memory, overexertion from daily/low-demanding tasks and by physical activity, as well as headache. Three participants had to reduce the working hours from a 40 working hours /week, to a 30 or 20 h/week). Pat. no. 1 had been unable to work for 3 months.

RESULTS

In the two female participants (Pat. no. 1 and Pat. no. 3) and one male participant (Pat. no. 4), both subjectively and objectively, a significant reduction in CFS syndrome and fatigue was observed and noted; resulting in better concentration performance, improved working memory, general mental endurance. Subjectively, they reported “clarity of mind”, “better quality of sleep” and “more energy”. A steady reduction in caffeine consumption, previously needed breaks in daily life, and a general qualitative improvement in concentrative endurance were reported as well. These improvements are well reflected in the final diagnosis. Together with the reduction of CFS symptoms, the mood stabilized, and the level of suffering was significantly reduced.

In one patient (Pat. no. 2), male, 22 years old, no improvement in symptoms was observed (Table 2).

Particular improvements were observed the FSS scale in following items: item 3 "I am easily fatigued" and item 9 "Fatigue interferes with my Work, Family or social life". In BDI -II, special reduction of symptoms in item 19 "Difficulty concentrating" and item 20 "Exhaustion and fatigue".

These results were also explicitly approved by the patients in the final evaluation meeting.

In (Pat. no. 3), the improvement in symptoms even allowed an increase in the number of working hours from 20 to 30 hours per week. In Patient 4 the reduction of fatigue and depressive mood was measurable with the BDI-II Test, which in one case decreased from the initial 22 points to the final 0 points after the treatment. The participant no. 4 (male, 28 years old), who had to reduce the number of working hours to 40%, could start his 40 h/week job again.

Table 1

Test Results of Patient no. 1

Test	**Pre-treatment**	**Post-treatment**
BDI-II	9 points	4 points
FSS	45 points	25 points
D2-R	within normal limits	within normal limits
Global Fatigue Skala (VAFS)	4	7
0 = being worst		
10 = being normal		

Note. Listing of pre-treatment and post-treatment test results of Pat. no. 1.

Table 2

Test Results of Patient no. 2

Test	**Pre-treatment**	**Post-treatment**
BDI-II	22 points	17 points
FSS	48 points	47 points
D2-R	far below average	far below average
Global Fatigue Skala (VAFS)	4	4
0 = being worst		
10= being normal		

Note. Listing of pre-treatment and post-treatment test results of Pat. no. 2.

Table 3

Test Results of Patient no. 3

Test	Pre-treatment	Post-treatment
BDI-II	19 points	9 points
FSS	57 points	16 points
D2-R	within normal limits	within normal limits
Global Fatigue Skala (VAFS)	5	10
0 = being worst		
10 = being normal		

Note. Listing of pre-treatment and post-treatment test results of Pat. no. 3.

Table 4

Test Results of Patient no. 4

Test	Pre-treatment	Post-treatment
BDI-II	22 points	0 points
FSS	60 points	12 points
D2-R	within normal limits	within normal limits
Global Fatigue Skala (VAFS)	2	9
0: being worst		
10= being normal		

Note. Listing of pre-treatment and post-treatment test results of Pat. no. 4

DISCUSSION & CONCLUSION

The results of this case study showed a positive effect of our treatment for 3 of 4 patients suffering from CFS induced by Post-Covid Syndrome. All patients were neurologically unsuspicious and received the same treatment with the identical frequency. We suspect that patient no 2, who could not show any improvement in symptoms, is a non-responder.

Severe depression was one of the exclusion criteria for this study. During the recruitment phase, many interested candidates had to be excluded due to either depression history or a present depression diagnosis, but it is difficult to distinguish between depression and CFS due to overlapping symptoms like lack of energy. We suspect that depression or depression history might indicate a higher vulnerability to develop psychological symptoms of post- COVID syndrome, which would go in line with the steadily reported association between depression and post-COVID syndrome.[14,15]

Furthermore, alternative rTMS frequency protocols should be considered. In this study we decided to use 1 Hz LF-rTMS over the right DLPFC because it showed significant effects in other inflammatory conditions like fibromyalgia. Nevertheless, other studies demonstrated efficacy of HF-rTMS over the left DLPFC in CFS.[12] Future studies could also look at the individual biomarkers of each patient to detect the personalized frequency stimulation rate.

Altogether, given the promising results, further research is indicated.

LIMITATIONS

The sample was very small and the influence of the two applied therapy methods cannot be distinguished from

each other. Larger and differentiated studies are needed, therefore this study will be continued. Furthermore, due to the circumstances of the clinic, no blinding of data was possible. No sham control group was involved.

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ABBREVIATIONS

CFS - Chronic Fatigue Syndrome DLPFC Dorsolateral Prefrontal Cortex

HF-rTMS - High-Frequency Repetitive Transcranial Magnetic Stimulation

LF-rTMS - Low-Frequency Repetitive Transcranial Magnetic Stimulation

NMDAR - N-Methyl-D-Aspartate Receptor

Pat. – Patient

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