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EC NEUROLOGY
Case Report

Clinical Effects of rTMS on Long COVID Neuropsychiatric Symptoms: Report of Case Series

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Received: October 22, 2021; **Published:** November 23, 2021

Abstract

Most of the patients who recover from COVID-19 acute infection will experience persistent peripheral and central neurological and psychiatric symptoms called long COVID, regardless of the severity of the initial infection. Repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation device, has shown to be a safe and effective tool to treat depression, chronic pain, fibromyalgia and fatigue syndrome among other neuropsychiatric disorders that seem to share some of the underlying mechanisms seen in long COVID. 20 - 30 high frequency rTMS over the left dorsolateral prefrontal cortex was performed in four patients suffering of long COVID using a H1 coil in one patient and a figure of eight coil in 3 patients. Fatigue severity scale, brain fog visual analogue scale, pain visual analogue scale, WHOQOL-BREF quality life scale and Beck depression inventory were measured prior, during and immediately after rTMS. After 20 - 30 sessions, rTMS showed significant beneficial effects on fatigue, pain, quality of life and cognitive but not on affective symptoms. No adverse events were reported on any of the patients..

Keywords: *Repetitive Transcranial Magnetic Stimulation (rTMS); Transcranial Magnetic Stimulation (TMS); Deep TMS; Long COVID; COVID 19*

Introduction

According to a recent review by Carod-Artal (2021), more than half of the patients who recover from COVID-19 experience neuropsychiatric symptoms in the post-acute phase, such as central and peripheral pain, fatigue, headaches, insomnia, dizziness, depression and cognitive difficulties; these long COVID symptoms are being reported in both, patients with mild initial infection as well as in patients who needed hospitalization or ICU admission during the acute phase [1]. The underlying mechanisms that have been proposed for these neuropsychiatric symptoms are systemic inflammation, neuroinflammation, microvascular thrombosis and neurodegeneration, which might induce brain hypometabolism [1].

Repetitive transcranial magnetic stimulation (rTMS) over the dorsolateral prefrontal cortex (DLPFC) has proven to induce anti-inflammatory effects, and to be an effective and safe treatment for neurologic and psychiatric disorders such as chronic pain, fibromyalgia, fatigue syndrome, depression, post-traumatic stress disorder and anxiety. To this day, there is no any effective treatment to improve long COVID symptoms.

Thus, we report the outcomes of the off-label use of high frequency rTMS (HF-rTMS) over the left DLPFC on four patients with brain fog, disabling chronic and diffuse pain and fatigue after recovering from COVID-19 initial infection [2-5].

Materials and Methods

Between January and April of 2021 four patients, one male and three females (aged 57 to 64 years), with long COVID symptoms 5 - 11 months after recovery from COVID-19 infection, received 20 to 30 sessions of rTMS.

rTMS protocol was set to deliver 3000 total pulses per session with a 10 Hz frequency, 4-second trains, 11-second intertrain interval, at 100% of the resting motor threshold (RMT) over the left DLPFC, using a Magstim® Rapid 2 system with a standard 70-mm figure-of-eight coil (F8c) (Magstim, Wales. UK) in three patients (patient 1, 2 and 3) and a BrainsWay Deep TMS™ system with an H1 coil (dTMS) (Brainsway LTD, Jerusalem, Israel) in one patient (patient 4). The RMT was defined as the lowest stimulus intensity to induce a visual contraction of right hand in five of 10 trials in the dTMS patient and a motor evoked potential >50 mV of the right first dorsal interosseous muscle for the rest of the patients. After giving oral and signed informed consent, the patients received Monday to Friday once a day sessions, except for the dTMS patient who received twice a day sessions, in consecutive weeks, for a total of 20 (patient 1) to 30 sessions (patient 2, 3 and 4).

Treatment outcomes were assessed using the fatigue severity scale (FSS), pain and brain fog visual analogue scales (p-VAS and bf-VAS [being 0 = no pain/no brain fog, and 10 = worst pain/brain fog imaginable]), WHOQOL-BREF quality life scale and Beck depression inventory (BDI) prior to and every rTMS 10 sessions.

Case Description

Patient 1 is a 60 year old woman with a 5-year history of chronic lower back pain and mild right carpal tunnel syndrome, who tested positive for COVID-19 which presented with mild symptoms such as fever, anosmia, dysgeusia, asthenia and effort dyspnea, treated only with paracetamol. Two weeks after recovery from acute phase, she developed persistent mild pain and heavy legs feeling sensation, asthenia, brain fog described as concentration "difficulties" and "mind going blank" and depression symptoms, and intermittent left tinnitus, upper limbs and lips paresthesias; symptoms persisted for eight months with no response to pharmacological treatment such as escitalopram paracetamol and anti-inflammatory medications (NSAIDs).

Patient 2 is a 64 year old woman with history of hypothyroidism treated with levothyroxine, admitted to our hospital with COVID-19 related bilateral pneumonia; After recovery from the acute phase, the patient developed many symptoms: persistent fatigue that made her feel impossible to walk more than 50 meters without resting, diffuse myalgias, brain fog described as "having troubles to remember conversations", and tension-type headache, and insomnia; symptoms persisted for four months and referred no response to melatonin; no other medication were prescribed.

Patient 3 is a 60 year old man was admitted to our hospital due to COVID-19 bilateral pneumonia. After recovery from the acute phase the patient developed persistent fatigue that made him unable to walk more than 50 meters without resting, asthenia, diffuse myalgias, tension-type headache, fluctuating thoracic throbbing pain, brain fog described as "difficulties performing daily activities if are not previously written in a notebook", and depression; these symptoms persisted for 11 months with no response to paracetamol nor amitriptyline.

Patient 4 is a 57 year old woman with previous history of dyslipidemia and high blood pressure, with COVID-19 related bilateral pneumonia treated at home with no further complications; 2 months after recovery of the COVID-19 infection the patient presented asthenia, diffuse arthralgias and myalgias, more severe on lower extremities, chest pain, severe fatigue, tension-type headache, brain fog described as "sustained attention difficulties and blurry vision", depression and insomnia. These symptoms showed severe fluctuations but persisted for seven months and reported only partial response to sertraline, pregabalin, melatonin and zolpidem; previously the patient did not tolerate amitriptyline.

Results

During and after the 20 - 30 sessions, no adverse events were reported by any patient.

Patient 1 reported that paresthesias disappeared, along with depression symptoms; legs pain markedly improved, being now mild and sporadic; brain fog also improved, reporting it once a week and lasting for half a day, and memory difficulties disappeared; tinnitus and asthenia persisted with no changes. FSS decreased from 61 (severe) to 50 (moderate), p-VAS from 8 to 3, bf-VAS from 8 to 2, BDI from 10 to 5 and WHOQOL-BREF increased from 74 to 81. Results were maintained for at least 3 months following treatment.

Patient 2 reported being able to walk up to 2 km with only mild to moderate fatigue; myalgias and headache disappeared, as well as brain fog and insomnia. After 30 rTMS sessions FSS decreased from 63 (severe) to 39 (moderate), p-VAS from 5.8 to 0, bf-VAS from 6.4 to 0, BDI from 11 to 1 and WHOQOL-BREF increased from 88 to 104. Results were maintained for at least 1 month following treatment.

Patient 3 reported no improvement. FSS decreased from 61 (severe) to 48 (moderate), p-VAS from 7.5 to 6.4, bf-VAS from 6.7 to 5.2, BDI from 34 to 34 (severe depression) and WHOQOL-BREF increased from 37 to 54. There is not yet any follow up on this patient.

Patient 4 expressed that her life was much better, fatigue had improved, insomnia, brain fog and depression symptoms had disappeared, she even stopped zolpidem. FSS decreased from 59 (severe) to 30 (mild), p-VAS from 8.1 to 1.1, bf-VAS from 6.6 to 0, BDI from 10 (mild depression) to 7 (no depression) and WHOQOL-BREF increased from 91 to 103. Results improved 2 months following treatment.

Figure 1 shows the changes of each patient scores before, during and after rTMS sessions.

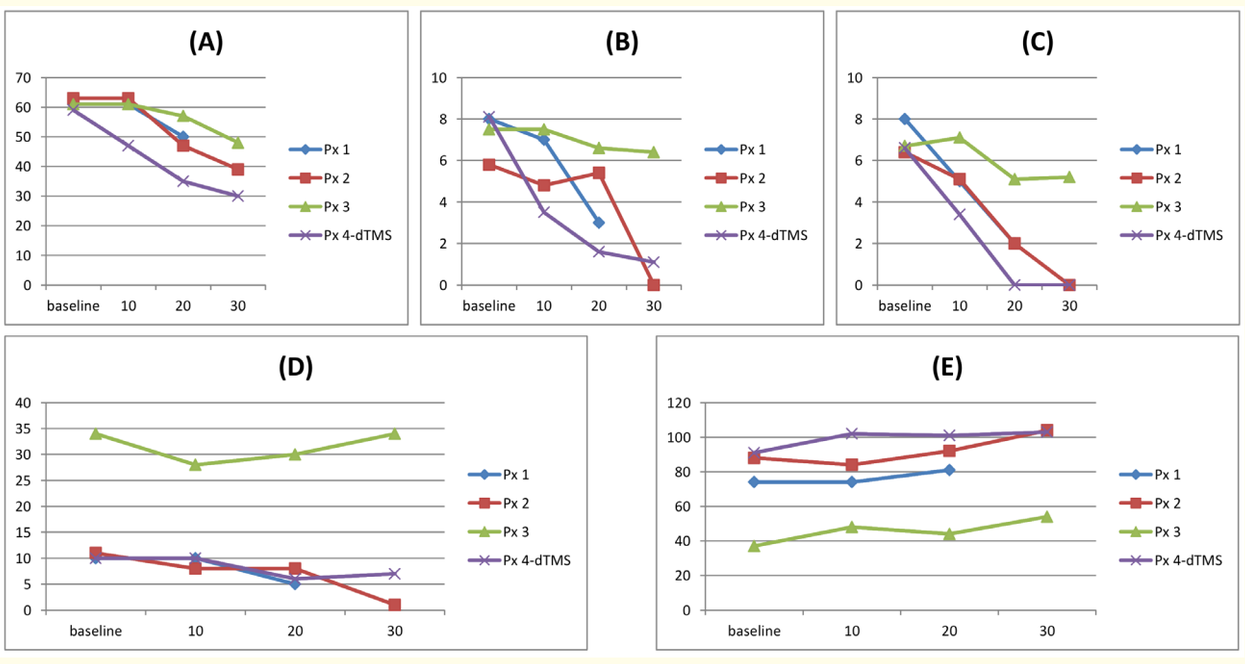

Figure 1: *Scores before and after rTMS sessions.*
(A) FSS, (B) p-VAS, (C) bf-VAS, (D) BDI and (E) WHOQOL-BREF scores before (baseline) and after 10, 20 and 30 rTMS (Px 1, Px2 and Px3) and dTMS (Px 4) sessions; Px 1 only received 20 sessions. Px = patient.

Discussion

Prior to rTMS sessions, patients 1, 2 and 4, showed similar scales scores on FSS, p-VAS, bf-VAS, BDI and WHOQOL-BREF scales; compared to patients 1, 2 and 4, patient 3 showed a high BDI score and a low WHOQOL-BREF score. Is important to mention that, although in patients 1, 2 and 4 the BDI reached the mild depression cut-off score, it was mostly related to the sleep, cognitive and fatigue items (items #16, 19 and 20).

After the rTMS treatment ended, patients 1, 2 and 4 expressed significant improvement in fatigue, pain, brain fog, depression symptoms and quality of life, with significant lower FSS, p-VAS, bf-VAS and BDI items #16, 19 and 20 scores, and higher WHOQOL-BREF score.

Although FSS and WHOQOL-BREF scores improved in patient 3, he referred no subjective improvements on any of the symptoms, having a slight improvement on the p-VAS and bf-VAS scores and no changes on the BDI score.

Only patient 3 showed important depression symptoms, reaching the severe depression cut-off before and after the rTMS treatment, which could explain why he expressed not having any improvement, even though his FSS and WHOQOL-BREF scales showed significant changes, supporting the idea that the down-regulation of pro-inflammatory cytokines might be in part, one of the underlying mechanisms of the rTMS effects on long COVID neuropsychiatric symptoms as proposed by Baptista., *et al*. (2020) [2].

These beneficial effects have also been found in patients diagnosed with fibromyalgia and chronic fatigue syndrome, who suffer similar symptoms and may share pathological mechanisms of long COVID patients [1,2,4,5]. As in chronic pain, fibromyalgia, chronic fatigue syndrome and depression patients, HF-rTMS over DLPFC in long COVID patients might be able to induce analgesic and anti-inflammatory effects by release of endogenous opioids and down-regulation of the spontaneous production of pro-inflammatory cytokines through the DLPFC-vagus connectivity; it is also important to mention that HF-rTMS could also ameliorate the affective and cognitive symptoms by up-regulating the hypometabolism state seen in the prefrontal cortex of long COVID patients, although in our report our patients did not showed significant improvement on affective symptoms.

Limitation of the Study

Our work has some limitations: the number of patients studied was small and no control group was used; cognitive symptoms (brain fog) were measured using a visual analog scale, and neuropsychological tests were not performed on the patients. Likewise, proinflammatory cytokines were not measured and neuroimaging tests were not performed to measure the state of brain metabolism. In spite of all this, we believe that as a pilot study it presents an undoubted value and allows to suppose that at least in some patients transcranial magnetic stimulation may have an application to relieve pain or depressive symptoms in patients with long term post-COVID Syndrome.

Conclusion

In conclusion, the use of HF-rTMS over the left DLPFC with a F8 or H1 coil was a safe an effective tool to improve fatigue, pain, quality of life and cognitive but not affective symptoms in our small report patients.

The known rTMS beneficial effects in disorders with similar symptoms and on this small series case report, show that rTMS is a potential safe and effective tool for long-COVID patients that needs to be explored in wider in order to obtain valid conclusions.

To our knowledge, this is the first report of the off-label use of rTMS as an adjuvant treatment for neuropsychiatric symptoms of long-COVID.

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Volume 13 Issue 12 December 2021