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Repetitive Transcranial Magnetic Stimulation for Major Depressive Disorder in Huntington Disease Patient with Improvement in Neuropsychiatric and Movement Symptoms: A Case Report

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Abstract
Introduction: Huntington disease (HD) is a progressive disorder characterized by significant neurodegeneration that results in severe neuropsychiatric symptoms and disordered movement. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive treatment that has been used in major depressive disorder (MDD) with great success. ***Case Presentation:*** We present a case of a patient with newly diagnosed HD, persistent MDD with suicidal ideation, and generalized anxiety disorder who was treated with rTMS and had sustained significant improvement of her mood disorder with additional improvement of her movement disorder. ***Conclusion:*** This result brings into question the use of rTMS to treat MDD and chorea in patients with HD, especially early in its course.

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Introduction

Huntington disease (HD) is an autosomal dominant genetic neurodegenerative disorder with well-known motor and neuropsychiatric effects. The neuropsychiatric effects are an early manifestation of HD, beginning up to 20 years prior to the movement manifestations [1]. There is a high rate of depression, suicidality, and overall morbidity due to the mental health impacts of the disease [2].

The pathophysiology behind HD is still under discovery, but many of its effects are attributed to the aberrant misfolding and subsequent deposition of toxic mutated huntingtin protein in the brain [3]. Some proposed mechanisms of the toxicity are changes in the microenvironment resulting in imbalanced neurotransmitters and excitotoxicity [4–7], increased free radicals and oxidative stress [6, 7], and decreased neural plasticity [4]. With these changes, the homeostasis of the brain is disrupted resulting in an inhibited capacity for recovery, adaptation, and connection. This, along with the deposition of huntingtin protein, causes the histological, neuropsychiatric, and physical exam features that are characteristic of the disease.

The current first-line treatment for major depressive disorder (MDD) in HD is a selective serotonin reuptake inhibitor with one study showing a 21.23% remission rate with its use [8]. This leaves much to be desired in treating the long-standing neuropsychiatric effects. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive treatment modality that uses a magnetic coil over the scalp to stimulate the underlying brain. It has been shown to balance neurotransmitters [9–11], decrease oxidative stress and excitotoxicity [9], and enhance neuronal plasticity and synaptogenesis [11]. Today, rTMS is primarily used in patients with severe MDD, in conjunction with at least one antidepressant medication, who have failed to respond to two or more pharmacological treatments in the past. There is potential for this treatment modality to be effective in a far greater variety of conditions, including neurodegenerative conditions like HD.

Case Description

We present a case report of a 68-year-old female with recently diagnosed HD who reports a significant decrease in depression, anxiety, and chorea following treatment with rTMS. The patient had a past mental health history of MDD, generalized anxiety disorder (GAD), posttraumatic stress disorder, and borderline personality disorder. She was diagnosed with HD in January 2023 with genetic analysis showing a 39 CAG repeat in one gene and no known family history of HD.

She originally presented for treatment with rTMS, prior to receiving her HD diagnosis, in June 2021 with severe symptoms of major depression and anxiety. These symptoms had been present for many years with frequent suicidal ideation (SI) without a plan or intent. She tried over eight medications including selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, atypical antipsychotics, bupropion, and lithium but felt they were all ineffective with undesirable side effects. She was found to be a good candidate for rTMS for her MDD because she had failed to respond to multiple pharmacological treatments. Prior to starting rTMS, the patient noted having daily SI and a "brain fog" that made it hard to think clearly and manage her finances. Additionally, she reported having poor sleep, low motivation, and overall poor quality of life. It was noted during the first rTMS treatment that she had frequent unintended sporadic movements. Her gait was ataxic, and she was unable to sit completely still with frequent movement in the arms, legs, trunk, face, and mouth.

The patient started right-sided rTMS 5 times per week for 30 treatments followed by a three, two, and one treatment(s) per week taper. Treatment involved a B-60 figure eight coil on the dorsolateral prefrontal cortex found using the BEAM method. Her motor threshold was found and rechecked on treatments 10, 20, 24, and 34. She was treated at 110% of her motor threshold at an amplitude of 45 for 15 min with 900 pulse total and 1 pps repetition rate and an interval of 0.1 s. She completed 41 treatments of rTMS from June to July 2021. Her progress was assessed using PHQ9 and GAD7 with her initial score being 25 and 19, respectively, and a final score of 2 and 4, respectively. During her first round of rTMS, she had been and continued taking 20 mg citalopram, 60 mg duloxetine, and 30 mg of buspirone.

In April 2023, she presented with recurrent symptoms of depression and anxiety that slowly redeveloped over the interval of 21 months. Prior to this, in January 2023, she was referred to a neurologist for abnormal movements and received a diagnosis of HD. Genetic testing showed a 39 CAG repeat on one allele and 20 CAG repeats on the other. She only became aware of her unintended movements in December 2022, although her daughter noticed them a few months prior.

In her second intake for rTMS, she reported that her previous treatment remarkably improved her mood disorder along with lessening her chorea. She was again found to be a good candidate for rTMS with her previous improvement and continued lack of response to pharmacological treatments alone. She restarted treatment in April 2023 and completed 36 treatments in June 2023. The second round of rTMS focused on the left side because she was more impacted by anxiety than depression at that time. She underwent 5 treatments per week for 30 treatments followed by three, two and one treatment(s) per week taper. A B-60 figure 8 coil was used on her left DLPRC, found using the BEAM method. She completed 36 treatments of TMS at a 120% motor threshold at an amplitude of 43. There were 75 pulse trains with 40 pulses, 10 pulses per second, and 11 s between trains. Her motor threshold was rechecked on treatment number 9 and 19 to maintain 120% motor threshold. During this treatment, she took 30 mg of buspirone daily with no changes. She reported no side effects during or after her rTMS treatments. After completing her 36 treatments with a taper, she continued with a maintenance regimen of one rTMS treatment per week. Her progress was assessed using PHQ9, GAD7, and the Unified Huntington's Disease Rating Scale (UHDRS®) [12]. The treatment team focused on the motor, behavioral, and functional portion of the UDHRS® for this patient. Her PHQ9, GAD7, and UDHRS® scores throughout treatment are displayed in Tables 1 and 2.

She completed four weeks of maintenance treatment at the last follow-up and, while still struggling with her social environment, felt that her rTMS treatments were successful. She was continued on a once per week left-sided rTMS maintenance regimen as described above. The maintenance regimen was working well for her, and her chorea was even less noticeable than one month prior. She remains capable of living independently with minimal symptoms and an increased feeling of purpose in her life. She was adherent to the treatment plan and denied having any adverse side effects.

From the patient's perspective, both rounds of rTMS significantly improved her mood, cognition, and quality of life. The brain fog she described was particularly debilitating, but she noticed that it appeared to lift after just one treatment, giving her back her independence. Furthermore, she notes that rTMS improved her motivation and desire to engage in hobbies and allowed her to maintain her independence in a fulfilling way. She is now optimistic about her future, whereas before she felt hopeless. The rTMS treatment succeeded when all other pharmacological treatments failed. The patient felt it important to add that she tried nine total treatments with Spravato in between her first and second rounds of rTMS that significantly reduced her SI. She discontinued the Spravato because she was unable to tolerate the effects during treatment and felt it had worked sufficiently to discontinue.

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Table 1. PHQ9 and GAD7 scores during the first and second rounds of rTMS and 1-month follow-up after the second round

	First round rTMS		Second round rTMS		1-month follow-up
	initial	final	initial	final	follow-up
PHQ9	25	2	15	11	7
Percent improvement*	92.0%		26.7%		53.3%
GAD7	19	4	7	6	7
Percent improvement*	78.9%		14.3%		0%

*Percent improvement was calculated by change in the score/original score.

Table 2. UDHRS® scores on initial versus follow-up assessment with percent improvement; second round of rTMS only

Section	Initial score	Final score	1-month follow-up	Overall percent improvement*
I: Motor	32	29	21	34.4%
III: Behavioral	58	26	20	65.5%
IV: Functional	22	23	23	4.54%
VI: Functional capacity	9	10	11	22.2%

*Percent improvement was calculated by change in the score/original score. Negative values indicate a regression, while positive values indicate an improvement.

Discussion

HD is a progressive genetic disorder that causes significant morbidity prior to ultimately taking the person's life. This case report adds to the growing literature indicating rTMS as a viable first-line treatment of the neuropsychiatric and possibly the movement disorder in HD.

Some of the key pathophysiological processes in HD are potentially attenuated and even reversed by rTMS [13]. The processes that may have led to this patient's successful response to rTMS are the metabolism and reduction of ROS [6, 7, 9], rebalancing of neurotransmitters [4–7, 9, 10], activation of the DLPC [5], and/or increased neuroplasticity [4, 11]. In HD, there is hypoactivation of the dorsal lateral prefrontal cortex [5], an area specifically targeted by rTMS for depression. The repetitive stimulation may work to rebalance the dysregulation in HD by strengthening healthy connections, creating new connections, and encouraging a more homeostatic microenvironment via cellular regulation and metabolism. This treatment modality is potentially an underutilized tool for HD, especially early in the disease process. Two other case reports have reported on the use of rTMS on a patient with HD. Both patients in these case reports showed alleviation of their neuropsychiatric symptoms with the latter showing potential reduction of their movement disorder [14, 15].

rTMS provides a unique opportunity to be used as an early intervention in patients with HD with potentially far better success than exclusive pharmacological treatment. Certain medications may be used in adjunct to rTMS to enhance the neuroplasticity effects. Examples are medications that work on the N-methyl-D-aspartate and brain-derived neurotrophic factor receptor such as ketamine and fluoxetine. Additionally, combination treatment with

psychotherapy and/or exercise therapy may further potentiate the effects of rTMS by inducing functional and epigenetic changes that are conducive to neuroplasticity. Medications that may dampen the effects of rTMS by suppressing neuronal activity are alcohol, benzodiazepines, and opioids. More clinical research needs to be done to assess the efficacy of rTMS on both the neuropsychiatric and movement portions of HD at different stages of the disease.

This case report was written using help from the CARE guidelines for case reports [16]. The CARE guideline checklist has been completed by the authors and attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000537750).

Limitations

Limitations of drawing conclusions from this case report are the inclusion of only one patient and the complex social environment that impacted the patients' PHQ9 and GAD7 scores.

Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and accompanying images. Ethical approval is not required for this case report in accordance with local guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Cheyenne Rahn and Kris Peterson were responsible for patient care. Cheyenne Rahn and Lizzie Lamb wrote the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data gathered or analyzed during this study are included in this case report. Further inquiries can be directed to the corresponding author.

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