Neuropsychiatr Invest. 2025; 63: 1-3

Case Report
10.5152/NeuropsychiatricInvest.2025.25006

Transcranial Magnetic Stimulation as an Alternative Treatment for Depression in Charcot–Marie–Tooth Disease

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ABSTRACT

Charcot–Marie–Tooth (CMT) disease is a hereditary peripheral neuropathy leading to progressive motor and sensory dysfunction. Patients with CMT frequently experience psychiatric comorbidities, particularly depression due to their physical limitations and decreased quality of life. Conventional pharmacological treatments for depression may be ineffective or poorly tolerated in this patient population, necessitating alternative therapeutic approaches. The case of an 18-year-old female with a prior diagnosis of CMT who developed recurrent, treatment-resistant depression is presented. Despite multiple pharmacological interventions, including fluoxetine and mirtazapine, the patient exhibited persistent depressive symptoms and medication intolerance. Given the limited efficacy of pharmacotherapy, she underwent transcranial magnetic stimulation (TMS) therapy as an alternative treatment option. The patient received intermittent theta burst stimulation targeting the left dorsolateral prefrontal cortex for 20 sessions over 4 weeks. Depression severity was assessed using the Hamilton Depression Rating Scale 17 (HAM-D17) and the Patient Health Questionnaire-9 (PHQ-9) before and after TMS treatment. Following TMS therapy, the patient demonstrated significant clinical improvement, with a reduction of over 50% in HAM-D17 and PHQ-9 scores. Additionally, she reported enhanced sleep quality and overall well-being, with no major adverse effects observed. This case highlights the potential of TMS as an effective and well-tolerated treatment for depression in patients with CMT. Given the challenges associated with pharmacological treatments in this population, TMS may serve as an alternative non-invasive intervention for individuals with CMT and comorbid depression. Further research is warranted to establish standardized protocols and efficacy in larger cohorts.

Keywords: Charcot–Marie–Tooth disease, iTBS, TMS, treatment-resistant depression

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Received: February 12, 2025
Revision Requested: May 5, 2025
Last Revision Received: August 5, 2025
Accepted: August 8, 2025
Publication Date: December 31, 2025

INTRODUCTION

Charcot–Marie–Tooth (CMT) disease is a hereditary peripheral neuropathy characterized by genetic mutations that impair the function of myelin and axons, affecting peripheral nerves outside the brain and spinal cord.[1] This leads to sensory and motor dysfunction. The clinical presentation of CMT varies among individuals but generally includes slowly progressive, symmetric muscle weakness and atrophy in distal extremities, sensory disturbances, skeletal deformities, and diminished or absent deep tendon reflexes.[2] These physical impairments, particularly chronic weakness and fatigue, can significantly affect psychological well-being, and depression secondary to reduced physical functionality is frequently observed in this patient population.[3] Pharmacological management of depression

Cite this article as: Garip B. Transcranial magnetic stimulation as an alternative treatment for depression in Charcot–Marie–Tooth disease. *Neuropsychiatr Invest.* 2025, 63, 0006, doi:10.5152/NeuropsychiatricInvest.2025.25006.

in patients with CMT is often complicated by factors such as side effects, drug-drug interactions due to polypharmacy, and the presence of somatic symptoms that may overlap with or exacerbate neurological complaints.[4] In light of these challenges, this case report presents the successful use of transcranial magnetic stimulation (TMS) therapy in a patient with CMT and comorbid depression, highlighting an effective non-pharmacological treatment alternative and underscoring the clinical significance of individualized neuromodulation strategies in complex patient populations.

CASE PRESENTATION

The patient is an 18-year-old female with a prior diagnosis of CMT disease, a hereditary neurological disorder characterized by progressive muscle weakness and sensory loss, primarily affecting the distal limbs. At the time of presentation, her CMT disease was stable, although she had experienced significant physical limitations. Over the course of her illness, she had undergone approximately 10 surgical procedures related to CMT, with the most recent surgery performed in 2020. Following this surgery, she experienced a prolonged period of immobility lasting approximately 1 year. The patient's psychiatric history began at the age of 14, when she was diagnosed with difficulty in anger control and anxiety disorder. To manage her symptoms, sertraline 50 mg/day was initiated. However, there was no improvement documented from this treatment.

Subsequent to this, in 2021, the patient began experiencing depression symptoms, including anhedonia, low energy, sleep disturbance, psychomotor agitation, and excessive worry and concentration problems, prompting a psychiatric consultation. Fluoxetine 20 mg/day was initiated for the treatment of depression and resulted in partial symptom improvement over a 6-month period. Although the patient experienced partial symptom improvement with fluoxetine 20 mg/day, no dose adjustment was made, and documentation regarding the rationale was unavailable in the medical record.

In October 2023, she presented with a relapse of depressive symptoms—persistent crying, fatigue, anhedonia, sleep disturbance, psychomotor agitation, and feelings of hopelessness and low energy. Fluoxetine 20 mg/day was reintroduced following psychiatric assessment.

Four days after reinitiating fluoxetine, the patient presented to the emergency department with tachycardia. Symptoms emerged shortly after starting the medication, raising suspicion of a fluoxetine-related adverse effect. However, no structural cardiac abnormalities were detected on electrocardiography (ECG), and no alternative causes of tachycardia were identified. Serial resting vital signs consistently showed a heart rate exceeding 100 bpm, peaking above 120 bpm, which caused significant distress and prompted 2 emergency visits. Given the temporal relationship and lack of other explanations, fluoxetine-induced tachycardia was suspected, and the medication was discontinued.

Due to recurring depressive episodes, mirtazapine 30 mg/day was initiated, but the patient showed no clinical response. As her symptoms worsened and daily functioning declined, she sought further evaluation at the clinic. A comprehensive review of her treatment history and side effect profile supported a diagnosis of recurrent, treatment-resistant depression. Given her intolerance to medications and insufficient response to pharmacotherapy, TMS was initiated as an alternative treatment strategy.

Transcranial Magnetic Stimulation Procedure

The TMS protocol was conducted using the MagVenture X100 device. Prior to treatment, a pre-evaluation was performed based on the pre-treatment risk assessment. Motor threshold measurement was carried out before the TMS application and repeated every week. The treatment intensity was determined to be 90% of the measured motor threshold. As part of the depression treatment protocol, the patient received intermittent theta burst stimulation (iTBS) consisting of 50 Hz bursts for 2 seconds, followed by an 8-second intertrain interval, with a total of 1800 pulses per session. A total of 20 treatment sessions were administered over the course of 4 weeks. This protocol was adapted from the Stanford Accelerated Intelligent Neuromodulation Therapy protocol, which utilizes iTBS and has received Food and drug administration (FDA) approval as a treatment approach for treatment-resistant depression.[5] The target brain region was determined using the Beam F-3 method, and the coil was placed to intersect the sagittal line at a 45° angle in the left dorsolateral prefrontal cortex. After the application, the patient was assessed for side effects based on current treatment guidelines.[6] Informed consent was obtained from the patient both for the initiation of TMS treatment and for the publication of this case report. Ethical approval was not required as this was a single-case report.

Psychiatric and Neuropsychological Assessments

Psychiatric evaluation was conducted using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (SCID-5),[7] and a diagnosis of major depressive disorder (MDD) was established based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision (DSM-5-TR) criteria.[8] Before the treatment, the Patient Health Questionnaire-9 (PHQ-9) and Hamilton-17 scales were administered to assess the severity of the patient's depression. The Clinical Global Impression-Improvement (CGI-I) Scale was applied to evaluate overall functionality. All psychometric assessments were conducted both before and after the TMS treatment. A reduction of 50% or more in the PHQ-9 and Hamilton Depression Rating Scale 17 (HAM-D17) scores was considered indicative of a positive response to the treatment.[9]

RESULTS OF THE TREATMENT

Before the initiation of treatment, the patient's HAM-D17 and PHQ-9 scores were recorded as 29 and 23, respectively. Following TMS therapy, a substantial reduction in depression severity was observed, with post-treatment scores improving to 11 and 9, respectively. The analysis of HAM-D17 and PHQ-9 scores before and after TMS therapy demonstrated an improvement exceeding 50%. Furthermore, the CGI score was assessed as 2 post-treatment, indicating notable clinical progress. The patient reported significant symptomatic relief, including improved sleep quality and a general reduction in feelings of sadness and hopelessness. Additionally, the patient described experiencing enhanced energy levels and an increased ability to engage in daily activities. Family members also reported noticeable improvements, citing a more positive attitude and greater social interaction. These qualitative observations align with the quantitative improvements in depression scores.

DISCUSSION

Charcot–Marie–Tooth disease is a hereditary neuropathy characterized by progressive peripheral nerve degeneration, often leading to substantial motor and sensory impairment. These physical

limitations can negatively affect patients' autonomy and quality of life, predisposing them to psychological comorbidities, particularly depression and anxiety.[10] Indeed, mood disturbances are frequently reported in individuals with CMT and are associated with both the burden of chronic disability and reduced social participation.[10]

Transcranial magnetic stimulation, a non-invasive neuromodulation technique, has emerged as an effective treatment option for patients with MDD, particularly those with treatment-resistant forms or who experience intolerable side effects from pharmacotherapy.[11,12] Transcranial magnetic stimulation exerts its therapeutic effects by modulating neural circuits implicated in mood regulation, primarily within the dorsolateral prefrontal cortex.[13,14] Given its favorable safety profile and efficacy, TMS represents a promising intervention for managing affective symptoms in neurologically vulnerable populations such as those with CMT.[15]

Given the significant psychological burden experienced by many patients with CMT, incorporating TMS into their treatment regimen may offer meaningful improvements in both mental health and overall functioning. This therapeutic approach not only addresses psychological symptoms but may also enhance patients' coping mechanisms in managing the physical limitations imposed by CMT, thereby potentially improving quality of life.[10,16,17] The present case highlights the potential utility of TMS as an adjunctive treatment for individuals with physical disabilities and treatment-resistant depression.[18] However, as a single-case report, these findings are inherently limited in their generalizability. Larger-scale, controlled studies are warranted to further evaluate the efficacy and safety of TMS in the CMT population and other patients with comparable neurological conditions.

In conclusion, this case report contributes novel clinical insights into the use of TMS for managing treatment-resistant depression in a patient with CMT disease. It underscores the importance of considering neuromodulation techniques in complex neuropsychiatric presentations and serves as a basis for future controlled studies in similar patient populations.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – B.G.; Design – B.G.; Supervision – B.G.; Resources – B.G.; Materials – B.G.; Data Collection and/or Processing – B.G.; Analysis and/or Interpretation – B.G.; Literature Search – B.G.; Writing Manuscript – B.G.; Critical Review – B.G.; Other – B.G.

Declaration of Interests: The authors declare that they have no competing interests.

Funding: The authors declared that this study has received no financial support.

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