Case Report

Low-frequency Repetitive Transcranial Magnetic Stimulation for Treatment of Tourette Syndrome: A Naturalistic Study with 3 Months of Follow-up

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ABSTRACT

The objective of this study is to report the effects of low-frequency repetitive transcranial magnetic stimulation (rTMS) in three patients with medication-refractory Tourette syndrome (TS) and over 3-month follow-up. A review of literature on the use of rTMS for the treatment of TS is also presented. Three patients with severe, medication-refractory TS and comorbid obsessive-compulsive disorder (OCD) in two of them, received an open-label trial of rTMS at 1 Hz frequency for 4-week duration. The first two cases of TS-OCD showed, on average, around 57% improvement in Yale Global Tic Severity Scale (YGTSS) scores (65% and 50%) and 45% improvement in Yale-Brown Obsessive-compulsive Scale (Y-BOCS) scores; however, the third case of pure-TS showed marginal improvement of 10% only. The improvement in TS-OCD patients with rTMS treatment was maintained at the end of 3-month follow-up, with an average reduction of about 49% (58% and 40%) and 36% observed in YGTSS and Y-BOCS scores, respectively. The present study supports the use of low-frequency rTMS to improve tics and OCD symptoms in patients with severe, medication-refractory TS-OCD. Further, the beneficial effects of rTMS treatment were maintained substantially over 3-month follow-up period.

Key words: *Obsessive-compulsive disorder, repetitive transcranial magnetic stimulation, Tourette syndrome*

INTRODUCTION

Tourette syndrome (TS) is a complex neuropsychiatric disorder and characterized by multiple motor and phonic tics. The majority of patients with TS experience complete or near-complete remission of tics, but in about 10%–20% of TS cases, tics persists or worsens during adulthood.[1] Motor and/or vocal tics are perceived by both the patients with TS and their family members as one of the most significant and bothersome symptoms of TS and that should be treated.[2] Management strategies commonly used for TS include reassurance, psychoeducation, cognitive behavioral therapy involving habit reversal training and exposure-response prevention, and pharmacotherapy with two main classes

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of drugs such as alpha-2 adrenergic agonists (guanfacine and clonidine) and antipsychotics (typical and atypical). However, approximately, one-third of patients with TS do not benefit from the abovementioned treatment strategies, and many of the medications used to treat tics produce significant side effects.[3] Therefore, novel, noninvasive, and safer treatment strategies such as repetitive transcranial magnetic stimulation (rTMS) need to be explored to reduce tics, especially in patients with severe, refractory TS. This is a noninvasive brain stimulation technique which uses repetitive brief, intense magnetic fields generated by a coil placed over the scalp producing an electric field in the underlying brain region through electromagnetic induction. In general, high-frequency (>5 Hz) rTMS promotes cortical excitability and low-frequency (1 Hz) rTMS inhibits cortical excitability.[4] Here, we report the effect of low-frequency rTMS (1 Hz) over bilateral supplementary motor area (SMA) in three patients with TS. A review of the literature on the use of rTMS for the treatment of TS is presented. The durability of the effects of rTMS in TS patients over 3-month follow-up is also reported.

METHODS

Three patients with severe, medication-refractory TS, and comorbid obsessive-compulsive disorder (OCD) in two of them (according to the International Classification of Diseases-10), presenting to the psychiatry outpatient clinic and given an open-label trial of low-frequency rTMS in accordance with the updated safety guidelines,[5] are described in this naturalistic study. Magstim Rapid TMS device (Whitland, UK) with a 70-mm figure-of-eight air film coil was used to administer rTMS. The resting motor evoked potential (MEP) was determined in accordance with the International Federation of Clinical Neurophysiology recommendations.[5] The resting motor threshold (RMT) was defined as the minimum stimulus intensity that produced an MEP in five out of 10 trials at rest. The stimulation parameters used were 1-Hz frequency, stimulation intensity at 110% of RMT, about 30 min sessions once/day (900 pulses/day), and 5 days/week (from Monday to Friday) for a total of 4 weeks (total of 20 sessions). The medications of all three patients were kept same for at least 12 weeks before and during the study period. The vertex was measured for each patient using the International 10–20 EEG System coordinates, and SMA was defined as 15% of the distance between inion and nasion anterior to the vertex on the sagittal midline. The coil was placed with the handle along the sagittal midline and pointing toward occiput to stimulate bilateral SMA simultaneously.

RESULTS

Case 1

A 24-year-old male with TS since 14 years of age and comorbid OCD for the past 4 years, presented with baseline Yale Global Tic Severity Scale (YGTSS) and Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores of 62/100 and 28/40, respectively. In treatment history, he had failed to respond to adequate dosages and durations of pharmacotherapy trials with typical and atypical antipsychotics (haloperidol up to 4 mg/day and risperidone up to 4 mg/day), selective serotonin reuptake inhibitors (fluoxetine up to 60 mg/day and clomipramine up to 300 mg/day), and tetrabenazine (150 mg/day). He was currently taking pimozide (6 mg/day), trihexyphenidyl (2 mg/day), fluoxetine (60 mg/day), and clonazepam (3 mg/day). The secondary causes of tics and OCD were ruled out. After obtaining informed written consent from the patient, he was given low-frequency rTMS following the study protocol. The patient reported decrease in tics and improvement in OC symptoms after a week of starting rTMS, with reduction in YGTSS and Y-BOCS scores to 22/100 and 14/40, respectively, at the end of 20 rTMS sessions. The changes in YGTSS and Y-BOCS score at 3-month follow-up period are described in Table 1.

Case 2

A 18-year-old male with TS since 8 years of age and comorbid OCD for the past 2 years, presented with baseline YGTSS and Y-BOCS scores of 86/100 and 26/40, respectively. In treatment history, he had failed to respond to adequate dosages and durations of pharmacotherapy trials with typical and atypical antipsychotics (pimozide up to 8 mg/day and risperidone up to 4 mg/day) and selective serotonin reuptake inhibitors (fluoxetine up to 60 mg/day and clomipramine up to 300 mg/day). He was currently taking fluphenazine (10 mg/day), trihexyphenidyl (2 mg/day), sertraline (200 mg/day), and clonazepam (6 mg/day). The secondary causes of tics and OCD were ruled out. After obtaining informed written consent from the patient, he was given low-frequency rTMS following the study protocol. The patient reported decrease in tics and improvement in OC symptoms after a week of starting rTMS, with reduction in YGTSS and Y-BOCS scores to 43/100 and 16/40, respectively, at the end of 20 rTMS sessions over 4 weeks. The changes in YGTSS and Y-BOCS score at 3-month follow-up are described in Table 1.

Case 3

A 15-year-old female with TS since 11 years of age and no comorbid psychiatric disorder, presented with baseline YGTSS score of 60/100. There was a

Table 1: Assessment of the Yale Global Tic Severity Scale and Yale-Brown Obsessive Compulsive Scale scores during the study period

Cases	YGTSS scores			Y-BOCS scores		
	Baseline	After 20 sessions of rTMS	After 3 months	Baseline	After 20 sessions of rTMS	After 3 months
1	62	22	26	28	14	16
2	86	43	51	26	16	18
3	60	54	56	-	-	-

rTMS – Repetitive transcranial magnetic stimulation; YGTSS – Yale Global Tic Severity Scale; Y-BOCS – Yale-Brown Obsessive Compulsive Scale

family history of tic disorder in her father and sister. In treatment history, she had failed to respond to adequate dosages and durations of pharmacotherapy trials with haloperidol (up to 4 mg/day), risperidone (up to 4 mg/day), and clonidine (up to 0.3 mg/day). At the time of presentation, she was taking pimozide (6 mg/day) and trihexyphenidyl (2 mg/day). Secondary causes of tic disorders were ruled out. After taking informed written consent from parent and assent from the patient, she was given low-frequency rTMS following the study protocol. There was no clinically significant improvement in her symptoms, with YGTSS score showing slight reduction to 54/100 at the end of 20 rTMS sessions over 4 weeks.

DISCUSSION

Although the exact pathogenesis of TS is not yet fully understood, emerging knowledge about neurocircuitry underlying TS can be used to guide and design focal brain stimulation techniques to treat TS. Recent neuroimaging studies have implicated overactivity of SMA to be responsible for tics and premonitory urges which seen in TS.[6,7] In our electronic literature search employing PubMed and Google Scholar databases, we found a total of nine clinical studies [Table 2] on the use of low-frequency rTMS for the treatment of TS, with maximum evidence for stimulation of bilateral SMA as expected. However, most of these human studies were of either open-label design or single-blind randomized crossover design, with no follow-up study periods assessing the durability of the effects of rTMS. A single double-blind, randomized, placebo-controlled trial was identified in our review, which showed no statistically significant difference between active and sham rTMS in reduction of tics.[16] This could be due to small number of patients (n = 20) or differences in stimulation parameters used in the study (3 vs. 4 weeks in the present study).

The first two cases of TS-OCD showed an average improvement of around 57% in YGTSS scores (65% and 50%) and 45% in Y-BOCS scores, that matches or exceeds the percent improvement seen with currently approved behavioral or pharmacological interventions for TS.[17] In contrast, the third case of pure-TS showed minimal improvement of 10% only. This could be due to the inherent differences between TS syndromes according to associated comorbidities, with recent neuroimaging studies supporting the role of unique networks in the TS-OCD syndrome as opposed to pure-TS.[18] This differential response with rTMS treatment may be explained by the involvement of different neural networks in TS as opposed to TS-OCD syndrome.[19] Similar findings have been reported in few previous studies of rTMS for the treatment of TS, with significant reduction of tics seen for TS-OCD but not for all TS patients.[12,15] The third case was of a younger girl and with a positive family history for tics disorder which might have contributed to the differential treatment response with rTMS, observed in the present study.

The rTMS sessions were safe and well tolerated with no significant side effects reported by none of the three patients. The beneficial effects of rTMS treatment in TS-OCD patients were maintained substantially at the end of 3-month follow-up, with an average reduction of about 49% (58% and 40%) and 36% (42% and 30%) observed in YGTSS and Y-BOCS scores, respectively.

CONCLUSIONS

The present study supports the use of low-frequency rTMS (1-Hz) over bilateral SMA as an adjunctive treatment to improve tics and OCD symptoms in severe, medication-refractory TS-OCD syndrome. The lack of treatment effect seen in pure-TS patient may assist in the identification of the TS population responsive to inhibition of the SMA in the future studies. The beneficial effects of rTMS treatment were maintained substantially over the 3-month follow-up period. In future, larger, double-blind, randomized placebo-controlled studies with higher number (total number of rTMS sessions and pulses delivered) of rTMS stimulation treatments and long-term follow-up periods should be done to confirm the findings of the present study and to determine the sustainability of the effects of rTMS and to explore the need of maintenance rTMS protocols for continuing the beneficial effects of rTMS treatment.

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Table 2: Review of clinical studies on use of repetitive transcranial magnetic stimulation for the treatment of Tourette syndrome

First author and year	Study design	Study population	Stimulation parameters (frequency, intensity, and number of pulses/day)	Target brain area	Result
Münchau, 2002[8]	Single-blind, placebo-controlled, crossover study	*n*=16 TS (7°CD) 12 males; 38±12.3 years	1-Hz, 80% of RMT, and 1200 pulses/day	Left MC or left PMC	No significant improvement with any of the rTMS conditions
Chae, 2004[9]	Single-blind, placebo-controlled, crossover study	*n*=8 TS (4°CD) 5 males; 14.9±16 years	1-Hz, 110% of RMT, and 2400 pulses/day	Left MC or left PFC	Improvement in tics and OCD with time, irrespective of site, or frequency of rTMS
Orth, 2005[10]	Single-blind, placebo-controlled, crossover study	*n*=5 TS (0°CD) 4 males; age range: 19-52 years	1-Hz, 80% of RMT, and 1800 pulses/day	Left PMC f/b right PMC Left PMC f/b sham right PMC Sham left PMC f/b sham right PMC	No significant improvement with any of the rTMS conditions
Mantovani, 2006[11]	Open-label study	*n*=10 (5°CD, 3 TS, 2 TS + OCD) 8 males; 33.5±13.5 years	1-Hz, 100% of RMT, 1200 pulses/day	Bilateral SMA	Significant improvement in tics and OCD symptoms
Mantovani, 2007[12]	Open-label study	*n*=2 TS + OCD; 16 and 22 years	1-Hz, 110% of RMT, and 1200 pulses/day	Bilateral SMA	Significant improvement in symptoms of TS and OCD
Kwon, 2011[13]	Open-label study	*n*=10 TS (1°CD) 10 males; 11.2±2.0 years	1-Hz, 100% of RMT, and 1200 pulses/day	Bilateral SMA	Significant improvement in tics and clinical global impression
Le, 2013[14]	Open-label study	*n*=25 TS (0°CD) 22 males; 10.6±2.2 years	1-Hz, 110% of RMT, and 1200 pulses/day	Bilateral SMA	Significant improvement in tics and comorbid conditions
Bloch, 2016[15]	Open-label study	*n*=12 TS (6°CD) 6 males; 32.6±12.7 years	1-Hz, 110% of RMT, and 1200 pulses/day	Bilateral SMA	No significant improvement in tics among the group as a whole; subgroup analysis of six patients with TS + OCD showed significant improvement in tic severity
Landeros-Weisenberger, 2015[16]	Phase 1: Randomized double-blind, sham-controlled trial for 3 weeks Phase 2: Additional open-label active treatment of Phase 1 randomized active rTMS arm for another 3 weeks	Phase 1: *n*=20 TS (5°CD) 16 males; 33.7±12.2 years Phase 2: *n*=7	1-Hz, 110% of RMT, and 1200 pulses/day	Bilateral SMA	Phase 1: No statistically significant difference in reduction of tic severity between active and sham rTMS Phase 2: Statistically significant reduction of 29.7% in tic severity compared to baseline

n – Sample size; OCD – Obsessive-compulsive disorder; RMT – Resting motor threshold; MC – Motor cortex; PMC – Premotor cortex; PFC – Prefrontal cortex; SMA – Supplementary motor area; rTMS – Repetitive transcranial magnetic stimulation; TS – Tourette syndrome; f/b – Followed by

Conflicts of interest

There are no conflicts of interest.

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