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Repetitive transcranial magnetic stimulation to treat benign epilepsy with centrotemporal spikes

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ABSTRACT

Objectives: To investigate the effects of low-frequency repetitive transcranial magnetic stimulation (rTMS) on patients with benign epilepsy with centrotemporal spikes (BECTS).

Methods: In this open pilot study, we enrolled four BECTS patients who had frequent seizures (at least 3 seizures during the 3-month baseline). After localizing sources of interictal epileptiform discharges (IEDs) with magnetoencephalography, IEDs-source-rTMS (1 Hz) with 500 pulses at 90% of resting motor threshold was applied for 10 weekdays in each patient. The primary outcome measure was the seizure-reduction rate after rTMS. Other outcome measures were the spike-wave index (SWI), behavioral evaluation, and adverse effects.

Results: All four patients received at least 3 months seizure-free after rTMS. Compared with baseline, SWI decreased significantly after rTMS in three patients (patient 1, 3 and 4) ($P = .002$, $P = .007$, and $P < .001$, respectively). Attention deficit identified in two patients in baseline recovered to the normal range after rTMS. No adverse effect was observed.

Discussion: Our preliminary observation provides a promising approach to reducing clinical seizures for BECTS with frequent seizures. Of importance, our data may provide a potentially novel method for the high prevalence of behavioral problems in BECTS patients via decreasing cortical hyperexcitability.

1. Introduction

Benign epilepsy with centrotemporal spikes (BECTS) is the most common focal epilepsy syndrome in children. The stereotypic nocturnal seizures involving arm and oral-facial tonic or clonic contractions as well as guttural sounds and drooling are commonly infrequent and outgrow in adolescence [1]. Traditionally, antiseizure medicine (ASM) is unnecessary for the majority due to the sparse seizures. Over the past few decades, increasing evidence has shown that cognitive and behavioral disturbances are common in BECTS patients despite the infrequent seizures and the benign property, including language impairments, reading and spelling difficulties, and attention deficits. Moreover, a proportion of patients have frequent seizures or even develop into the atypical form of BECTS [2]. ASM, however, is demanded if seizures are frequent or for patients with atypical form.

Massive interictal epileptiform discharges (IEDs) over the centrotemporal regions during non-rapid eye movement sleep and occasional wakefulness are the electrophysiological signature of BECTS, representing the intrinsic cortical hyperexcitability [3]. The normalization of the cortical excitability, therefore, is the key to resolving the clinical profiles of BECTS. However, whether and how well the current available ASM can suppress the distinct pathological discharges is still a matter of debate [1]. Clinically, patients with frequent seizures or atypical form tend to be drug-resistant. To date, the optimum intervention has yet to be identified.

Repetitive transcranial magnetic stimulation (rTMS) has been successfully applied to treat a wide range of neuropsychiatric disorders in recent years [4]. Although the mechanism of rTMS is not fully understood, low-frequency rTMS is thought to decrease the cortical excitability at the stimulated site and functionally connected remote areas [5]. Considering the therapeutic nature of rTMS, we hypothesized that rTMS can normalize the cortical hyperexcitability and thereby attenuate the electrophysiological aberrant and ameliorate seizures for BECTS patients. Here, we assess the efficacy of low-frequency rTMS for the treatment of BECTS patients.

2. Methods

Four BECTS patients who had frequent seizures (no less than 3 times within the past three months) were recruited between August 2020 and June 2021, in Xuanwu Hospital. The study protocol was approved by the Ethics Committee at Xuanwu Hospital. Written informed consent was obtained from legal guardians.

The patient evaluation and treatment pipeline were shown in Fig. 1A. The treatment phase encompassed a 3-month baseline evaluation period, followed by 2 weeks treatment period when the patients received low-frequency rTMS. The remaining 6 months was the clinical follow-up period.

Pre- and post-stimulation EEG recordings were performed (Fig. S1A). After localizing sources of IEDs with magnetoencephalography (Fig. S1B), each patient was treated with once-daily

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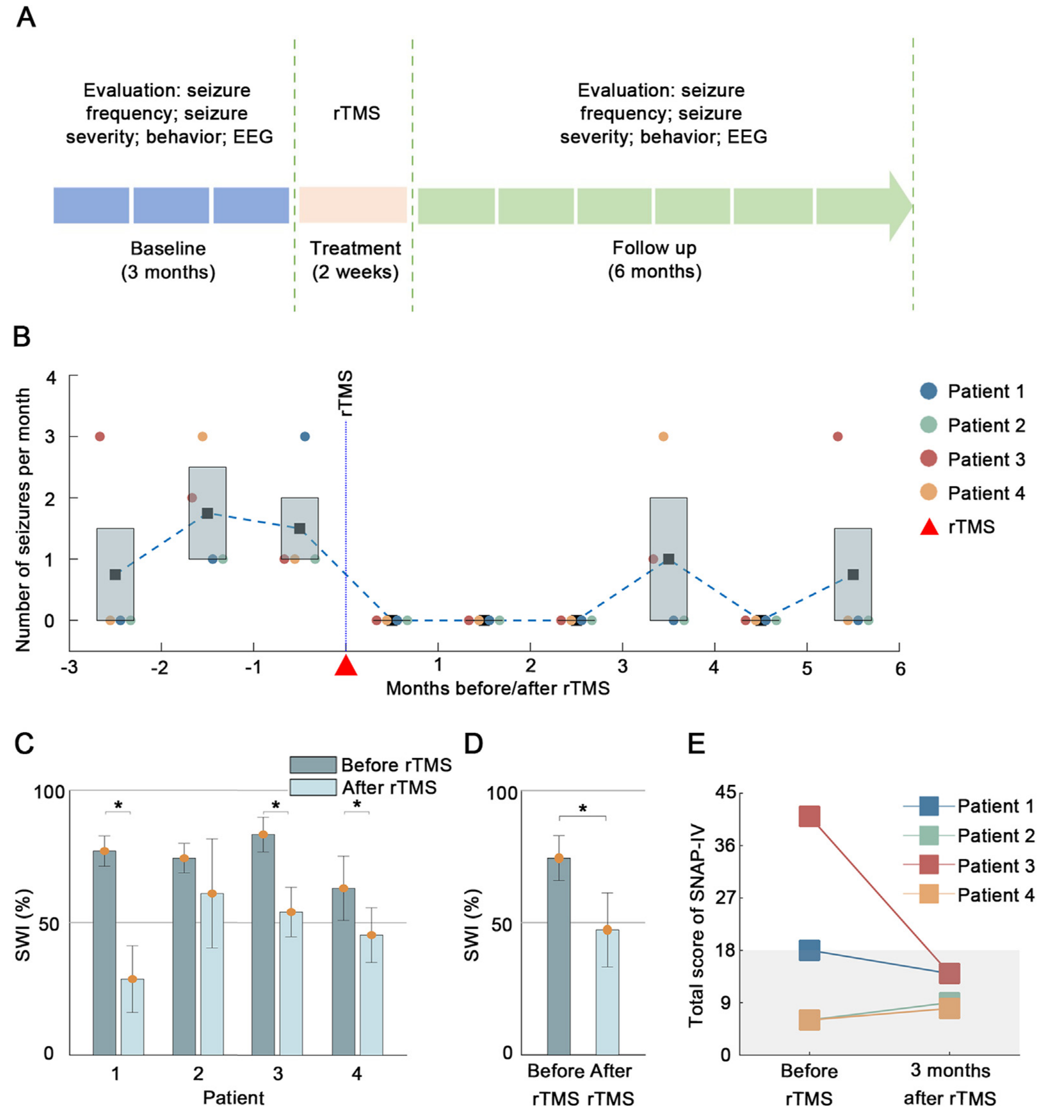

Fig. 1. Patient Evaluation and Outcome. (A) Flowchart overview of the study design. (B) Distribution of the number of seizures before and after the rTMS treatment. Boxplot shows the distribution of numbers of seizures per month for all four patients during the 9-month investigation. Boxplots display the interquartile range (edges of the box). The mean is expressed by filled squares connected by dashed line. The color-coded scatters show the number of seizures per month for each patient. The red triangle indicates the rTMS treatment. (C) SWI. Each bar represents the first five continuous 1-min sleep blocks of data from a single patient. The comparison of SWI was significant in 3 of the 4 patients ($P = .002$; $P = .257$; $P = .007$; $P < .001$). (D) Mean SWI. The average of SWI significantly decreased from pre-rTMS to post-rTMS at the group level ($P = .04$). The error bars indicate standard error. The asterisk (*) denotes a statistically significant difference ($P < .05$). (E) SNAP-IV scores. The data are demonstrated as line graphs with each line representing a single individual. The gray area with a total score of <18 represents the normal attention capacity. Abbreviations: SWI, spike-wave index; SNAP-IV, Swanson Nolan and Pelham-IV Rating Scaler. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

sequential bilateral IEDs-source-rTMS sessions, 5 times/week for 2 weeks (1 Hz, 90% resting motor threshold, 500 pulses per hemisphere) via a figure- 8 coil (Figs. S1C and D).

Caregivers were requested to record every seizure during the 6-month follow-up. Additionally, the spike-wave index (SWI) was measured as the mean percentage of one-second bins occurring in 1 minute with ≥1 spike and wave within the first 5 continuous minutes after sleep onset. The 18-item Swanson Nolan and Pelham-IV Rating Scaler (SNAP-IV) was assessed the day before and 3 months after rTMS to detect the behavioral outcomes. Paired t-tests were used to determine the significance of data from the same patient or group. Statistical significance was set at P-value < .05.

See the eMethods in the Supplement for further details concerning study design, technical information and statistical analysis.

3. Results

The general clinical characteristics of all four patients are summarized in Table S1. The mean (range) age of seizure onset was 5.75 (5–7) years. All patients presented predominantly nocturnal focal seizures manifesting with altered sensory-motor function of the face, unilateral facial or arm clonic movements as well as hypersalivation, and 3 of them combined with generalized tonic-clonic seizures.

Remarkably, all patients experienced at least three months seizure-free without ASM alteration, among them, two patients reported 6 months seizure-free (Fig. 1B). Regarding the impact on IEDs, SWI decreased significantly after rTMS in three patients (patient 1, 3 and 4; $P = .002$, $P = .007$, and $P < .001$, respectively), and in the other patient the decrease trend was seen that did not reach the statistically significance (patient 2; $P = .257$) (Fig. 1C).

At the group level, the mean SWI also remarkably decreased from pre-stimulation to post-stimulation (74% versus 47%, P = .04) (Fig. 1D). Additionally, by quantification evaluation, attention deficit identified in two patients in baseline (total score of SNAP-IV ≥ 18) recovered to the normal range after rTMS (Fig. 1E). Finally, no adverse effect was reported during and after rTMS.

4. Discussion

Currently, little attention has been paid to the treatment of most BECTS patients due to sporadic seizures, while the optimum approach to decrease the Rolandic hyperexcitability remains lacking [1]. To our knowledge, this is the first clinical intervention using rTMS to treat BECTS.

So far, studies regarding the effectiveness of ASMs in respect of their ability to suppress epileptiform discharges therefore ameliorate seizures in BECTS have been scarce. Previous data revealed that both levetiracetam and sulthiame have beneficial effects on EEG normalization [6,7]. However, in view of the potential side effect of sulthiame causing cognitive deterioration [8] and the relatively few adverse effects of levetiracetam, many clinicians use levetiracetam as the first-line medication. All patients in the present study had persistent seizures despite treatment with levetiracetam or even more ASMs. rTMS improves the seizures in these patients by suppressing IEDs and thus provides a new, non-pharmacological, and easily accessible approach to treat BECTS patients. Given the limitation of the small sample size, future prospective, randomized, and sham-controlled studies are required to provide more definitive evidence.

Consistent with previous reports [9,10], the favorable effects on suppression of seizures after low-frequency rTMS demonstrate an off-line long-lasting trend in the present result, which might largely ascribe to the cortical long-term depression induced by rTMS [5].

Generally, our preliminary observation reveals the therapeutic effects of rTMS to reduce clinical seizures for BECTS with frequent seizures. Of importance, our data may provide a potentially novel method for the high prevalence of behavioral problems in BECTS patients via decreasing cortical hyperexcitability.

Contributors

LKR, LH and YPW had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. HL, GYJ, LQ, JC and JLD contributed to acquisition and analysis of data. GYJ, JLD and JC contributed to drafting of the manuscript. All authors revised the manuscript critically for intellectual content and approved the final version. JC, JLD, DW and GYJ contributed to Statistical analysis. LKR contributed to the conception and design of the work.

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Ethics approval

This study was approved by the Ethics Committee at Xuanwu Hospital. Before inclusion, written informed consent was obtained from the legal guardians of each patient. This study and all authors followed the World Medical Association's Declaration of Helsinki.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2022.04.003.

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