Journal of the Neurological Sciences 392 (2018) 56–62

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Effects of cerebellar magnetic stimulation on chronic post-lateral medullary infarction dizziness: A proof-of-principle cohort study

Ken Johkura[a,*], Yosuke Kudo[a], Eriko Sugawara[a], Kosuke Watanabe[a], Tomoki Nakamizo[a], Masahiro Yamamoto[a], Kazumitsu Amari[b], Koji Takahashi[c], Osamu Tanaka[c]

[a] Department of Neurology, Yokohama Brain and Spine Center, Yokohama, Japan
[b] Department of Neuroendovascular Therapy, Yokohama Brain and Spine Center, Yokohama, Japan
[c] Department of Clinical Laboratory, Yokohama Brain and Spine Center, Yokohama, Japan

ARTICLE INFO

Keywords:
Lateral medullary infarction
Dizziness
Repetitive transcranial magnetic stimulation
Cerebellum
Vestibulo-ocular reflex

ABSTRACT

Background and purpose: Lateral medullary infarction (LMI) sometimes causes long-lasting dizziness. Although the precise mechanism of chronic post-LMI dizziness is unknown, a cerebellar control disorder of the vestibulo-ocular reflex (VOR) has been reported in such patients. We conducted a proof-of-principle cohort study to assess the potential efficacy of cerebellar repetitive transcranial magnetic stimulation (rTMS) as treatment for chronic post-LMI dizziness.

Methods: We first applied cerebellar rTMS in healthy volunteers (n = 11) and showed that cerebellar intermittent theta burst stimulation (iTBS) affected vestibulocerebellar neural activity. Then, between September and December 2015, we enrolled six patients (aged ≥ 20 years) with chronic post-LMI dizziness (duration ≥ 6 months), applied cerebellar rTMS (iTBS for 5 days), and followed these patients up for up to 25 months for clinical symptoms (Dizziness Handicap Inventory [DHI]), signs (nystagmus), and VOR gain.

Results: Four of the six patients completed the study without complications. After rTMS, DHI scores were reduced (mean pre-rTMS DHI score minus post-rTMS DHI score was 13.0 [P = 0.036]) with disappearance of the ipsilesional nystagmus characteristic of the post-LMI dizziness. Reduction in the absolute VOR gain (mean pre-rTMS gain minus post-rTMS gain in the ipsilesional direction was 0.135 [P = 0.036] and that in the contralesional direction was 0.137 [P = 0.031]) were also associated with reduced DHI scores. Relative cerebellar blood flow to the brainstem was increased in four of five patients. The effects of cerebellar rTMS did not always persist, and three of four patients elected to undergo more than one rTMS series. The repeat cerebellar rTMS treatments had same beneficial effects.

Conclusion: Our study showed, for the first time, the potential efficacy of cerebellar rTMS for treatment of chronic post-LMI dizziness. The short duration of the cerebellar rTMS effects can be compensated for by repeating the rTMS treatment every few months. Further large-scale randomized studies are warranted to confirm our findings.

1. Introduction

Lateral medullary infarction (LMI) syndrome, or Wallenberg syndrome, is a well-known vascular syndrome, usually caused by occlusion of the posterior inferior cerebellar artery or vertebral artery [1]. In the acute phase of LMI, vertigo, dizziness, and/or disequilibrium, usually associated with other neurologic symptoms such as gait disturbance, dysphagia, hoarseness, and impaired facial and contralateral limb/body sensation, is commonly seen [2]. The dizziness (including vertigo and disequilibrium) accompanying LMI often persists for a long time [3] and can lead to serious psychosocial sequelae [4]. There is, however, no established treatment for chronic post-LMI dizziness.

Various types of nystagmus have been reported in patients who have suffered an LMI [5–7]. To determine the characteristic pattern of nystagmus associated with chronic post-LMI dizziness, we recently compared nystagmus in patients with and without post-LMI dizziness; ipsilesional nystagmus was characteristically associated with chronic post-LMI dizziness, regardless of the test conditions [4]. The nystagmus in LMI patients involves disruption of ipsilateral cerebellar inhibition of the velocity-storage mechanism of the vestibulo-ocular reflex (VOR) [7], so pathological disinhibition of the velocity-storage mechanism might in part explain chronic post-LMI dizziness [4]. If such disruption

* Corresponding author at: Department of Neurology, Yokohama Brain and Spine Center, 1-2-1 Takigashira, Isogo-ku, Yokohama 235-0012, Japan.
E-mail address: ke00-johkura@city.yokohama.jp (K. Johkura).

https://doi.org/10.1016/j.jns.2018.07.007
Received 16 April 2018; Received in revised form 21 June 2018; Accepted 8 July 2018
Available online 10 July 2018

in the cerebellar modulation of VOR plays a role in post-LMI dizziness, we may be able to ameliorate the dizziness by enhancing the effect of the cerebellum on VOR function via cerebellar stimulation.

Repetitive transcranial magnetic stimulation (rTMS) is used therapeutically as a non-invasive means of modulating excitability of the human brain. Typically, low-frequency stimulation of 1 Hz reduces neural activity (resulting in long-term depression) [8], whereas high-frequency stimulation of > 5 Hz increases neural activity (resulting in long-term potentiation) [9]. Theta-burst stimulation (TBS), 3 pulses at 50 Hz repeated at intervals of 200 ms, in comparison to standard rTMS protocols, can induce longer lasting changes in human brain excitability [10]. rTMS has been applied in the treatment of post-stroke patients; for instance, rTMS with long-term potentiation effects is applied to the lesioned hemisphere to enhance neural activity [11], and rTMS with long-term depression effects is applied to the non-lesioned hemisphere to reduce abnormally high interhemispheric inhibition in patients with chronic stroke [12]. rTMS targeting the cerebellum has gained attention for treatment of post-stroke sequelae [13]. We conducted a proof-of-principle cohort study in which we applied rTMS over the cerebellum and investigated its effect over time on chronic post-LMI dizziness.

2. Methods

2.1. Testing the effects of cerebellar rTMS on the vestibular-oculomotor system in healthy volunteers

Before applying rTMS to patients suffering from post-LMI dizziness, we verified the effects of rTMS applied over the cerebellum in 11 healthy volunteers (Supplement 1). We placed a double-cone coil 2 cm below the inion [14,15] and, using a high-speed stimulator (Magstim Rapid^2, Magstim Inc., Whitland, UK), performed intermittent theta burst stimulation (iTBS, i.e., a 2-s TBS train repeated every 10 s) for a total of 600 pulses [10] at an intensity of 80% of the descending pyramidal tract resting motor threshold (n = 5) [14]; 1-Hz stimulation for a total of 1200 pulses at an intensity of 80% of the descending pyramidal tract resting motor threshold (n = 2); 5-Hz stimulation for a total of 600 pulses at an intensity of 80% of the descending pyramidal tract resting motor threshold (n = 1); or sham stimulation (n = 3). Of these test protocols, only iTBS induced horizontal geotropic positional nystagmus and a reduction in the absolute VOR gain. Usually, cerebellar dysfunction induces horizontal apogeotropic positional nystagmus and an increase in the absolute VOR gain [16]. Both the direction of the nystagmus and the change in VOR gain induced by cerebellar iTBS in our volunteers were opposite those caused by cerebellar dysfunction. Thus, we were convinced that iTBS increases cerebellar neural activity in healthy persons (Supplement 1). Based on these results in healthy volunteers, we chose iTBS as the means of cerebellar stimulation.

2.2. Testing the effects of cerebellar rTMS on the vestibular-oculomotor system in patients with chronic post-LMI dizziness

Once we confirmed the effects of iTBS in the healthy volunteers, we carried out the safety and proof-of-principle cohort study. The study was conducted at a single center, Yokohama Brain and Spine Center, under a protocol that was approved by the institutional ethics committee. All study patients provided written informed consent for their participation after the study protocol and associated risks were explained to them. The study is registered with UMIN-CTR (UMIN000018761).

2.3. Patients

Patients with chronic post-LMI dizziness were recruited for participation in the study between September and December 2015. Patients were considered eligible if they were at least 20 years of age, if 6 months or more had passed since the onset of LMI, and if the dizziness had not improved at all during the 6 months prior to recruitment. Patients with a previous neurological or psychological disorder or a peripheral vestibular disorder such as benign paroxysmal positional vertigo, vestibular neuritis, or Ménière's disease were excluded. Patients in whom rTMS was contraindicated, such as those with a permanent pacemaker or a history of seizures, were also excluded. Eventually, six patients were enrolled in the study.

2.4. Procedures

Patients underwent five sessions of rTMS, i.e., iTBS of the cerebellum once a day for 5 consecutive days. For each patient, the iTBS was performed with the same device and at the same settings used in the healthy volunteers (a 2-s TBS train repeated every 10 s, for a total of 600 pulses at 80% descending pyramidal tract resting motor threshold recorded in the first dorsal interosseous muscle electrode), via high-speed stimulator (Magstim Rapid^2, Magstim Inc., Whitland, UK) and double-cone coil placed 2 cm below the inion [10,14,15]. No specific rehabilitation was combined with the rTMS treatment, but nonspecific gymnastic and walking exercises that patients performed before rTMS were continued during and after the rTMS treatment. Because the effect of rTMS generally lasts only several weeks at most [17], patients who requested it were allowed additional rTMS sessions at intervals of 1 month or more.

2.5. Assessments

Before and after the 5-day rTMS treatment, dizziness, nystagmus, VOR gain, and regional cerebellar blood flow were evaluated. Dizziness, nystagmus, and VOR gain were evaluated monthly thereafter. Dizziness was evaluated by means of the Dizziness Handicap Inventory (DHI), which consists of 25 questions representing the effects of dizziness on daily life in three domains: functional, emotional, and physical [18]. Nystagmus was recorded in darkness under spontaneous, head-shaking, and positional test conditions by means of video-oculography (VOG) performed with the use of Frenzel goggles and a built-in charge-coupled camera with infrared illumination [4]. Head-shaking nystagmus was induced by a passive head-shaking maneuver; the patient's head was manually shaken horizontally in a sinusoidal fashion at a rate of about 2.8 Hz with an amplitude of about ± 10 degrees for 15 s [4,7]. The horizontal VOR was recorded in darkness by means of a VOG recording and analysis system (IRN-2, Morita Mfg. Corp., Kyoto, Japan) and use of a rotating chair with a headrest (S-II, Nagashima Medical Instruments Corp., Tokyo, Japan) [4]. The chair was programed to rotate in sinusoidal fashion for 30 s (frequency, 0.6 Hz; amplitude, 60 degrees). VOR gain was determined as the ratio of eye velocity to head velocity [4]. Corresponding changes in regional cerebral blood flow (CBF) in the cerebellum were examined by means of ^{99m}Tc-ECD brain perfusion single-photon emission computed tomography (SPECT). Regional CBF was quantified by means of FineSRT, a fully automated regional CBF quantification software (Supplement 2) [19,20]. Our therapeutic target was a change in cerebellar control over the brainstem vestibular system by cerebellar rTMS. Thus, we calculated the ratio of cerebellar blood flow to brainstem blood flow (CBF ratio) to detect relative CBF change (Supplement 2) [21]. Change in the CBF ratio, i.e., difference between the CBF ratio obtained before and that obtained after 5-day rTMS treatment was determined for each patient. Because the radioisotope injection made measuring CBF invasive, change in the CBF ratio was determined only in relation to the initial 5-day rTMS treatment even if the patient received later rTMS treatments.

2.6. Statistical analysis

Differences between pre- and post-rTMS DHI scores and VOR gains were analysed by Wilcoxon signed rank test. All statistical analyses