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Beneficial effects of cerebellar rTMS stimulation on a patient with spinocerebellar ataxia type 6

Spinocerebellar ataxia type 6 (SCA6), an autosomal dominant ataxia involving mutations in the *CACNA1A* gene, is characterized by progressive ataxia together with cerebellar atrophy and selective Purkinje cell degeneration [1]. To date, no curative pharmacological therapy for this neurodegenerative disease has been approved. Repetitive transcranial magnetic stimulation (rTMS) over the cerebellum may have the potential to be a therapeutic tool in cases of cerebellar degeneration, exerting its effects probably by increasing cerebellar blood flow and improving cerebellar function [2]. Herein, we report the effect of cerebellar rTMS treatment on a patient with a genetic diagnosis of SCA6. Continuous follow-up with the patient was conducted for 18 months.

In this case report, the subject was a 34-year-old female patient with a 2-year history of gait and speech difficulties. Prior to her first hospital visit, the patient had developed gait instability, followed by the development of unclear and slurred speech. She decided to seek medical attention when she realized that her symptoms worsened progressively, affecting her daily life. On admission, neurological examination revealed truncal and limb ataxia, a wide-based gait, dysarthria, and horizontal gaze nystagmus. Deep tendon reflexes were normal and no pyramidal tract signs were observed. Brain magnetic resonance imaging (MRI) revealed significant cerebellar atrophy, which was congruent with the genetic analysis, revealing the presence of abnormal CAG trinucleotide repeats in the *CACNA1A* gene. Together, these findings confirmed a diagnosis of SCA6. Total score of International cooperative ataxia rating scale (ICARS) was 41/100 and Scale for the assessment and rating of ataxia (SARA) yield a sum score of 14/40. All sub-scores of ICARS and SARA are shown in Fig. 1. The patient's movements were video recorded (see supplemental data). Cerebellar rTMS has been widely reported to be useful for treating ataxia [3]. After explaining the benefits and the potential risks of rTMS to the patient, written informed consent was obtained prior to the commencement of treatment regimen. We conducted a trial of high-frequency rTMS over the cerebellum. This trial was approved by the local Ethics Committee. TMS was delivered using MagPro X100 (MagVenture, Denmark). The figure-8 coil was placed over Iz (international 10–20 systems) and pulses at 100% intensity of the resting motor threshold were administered at 10 Hz (1 s trains, 10 s intertrain interval, 1500 pulses/session). The delivery regimen consisted of 20 sessions, conducted once daily for 5 days a week. After the 5th session, we observed a mild improvement, characterized by more stability in gait and stance. Later, the patient improved progressively during the treatments; her aforementioned slurred and unclear speech was also improving. Clinical assessments were performed immediately after the last session of rTMS therapy. The post-intervention ICARS total score of 16/100 indicated that sub-scores in posture and gait disturbances, kinetic functions and speech disorders were meaningfully and significantly decreased after rTMS treatment. No improvement was observed in the oculomotor disorders. The total post-intervention SARA score was 6/40, and a decrease in all the sub-scores was observed, except for finger chase (Fig. 1). Afterwards, no recurrence of ataxia symptoms was observed and the patient was able to return to her normal daily routine during the follow-up. At 18-months post-intervention, after the last session of rTMS, neurological assessments were once again performed. The total ICARS and SARA score were 11/100 and 2.5/40 respectively, and the sub-scores are shown in Fig. 1. Further improvement

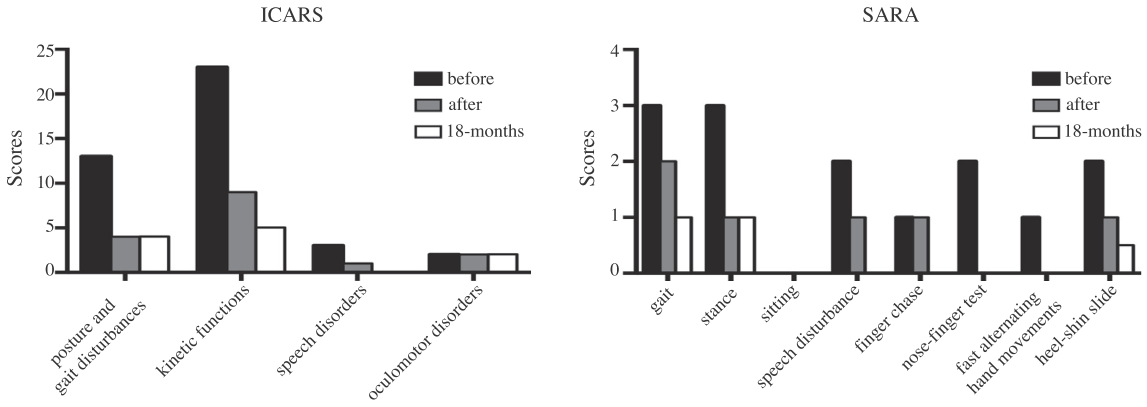

Fig. 1. Sub-scores of ICARS and SARA before, immediately after, and at 18-months after rTMS.

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of motor and speech function was observed at this time. It is noteworthy that the patient was not undergoing any other SCA-focused therapies prior to, during, and after the rTMS treatment.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.brs.2018.12.225.

The durability of the positive effects is a point of great importance in rTMS treatment; the ideal therapeutic intervention will result in long-lasting effects. A prior study demonstrated improvements in mobility, standing postural control, gait kinematics, and muscle coordination were maintained for 6 months after intervention in a patient with a probable diagnosis of idiopathic late-onset cerebellar atrophy who was treated with low-frequency TMS over multiple loci of the cerebellum [4]. In our study, we report on a patient with a definitive diagnosis of SCA6 who benefited from high-frequency rTMS over the middle cerebellum; the benefits ranged from muscle coordination in limbs and trunk, to speech. After our 18-month follow-up, we demonstrated the maintenance of these benefits. Although the precise physiological mechanisms underlying the long-term effects of cerebellar rTMS in alleviating ataxia remain unclear, such maintenance of benefits can possibly be reflective of the neural circuit remodeling that was induced by rTMS treatment [5]. In patients with inherited spinocerebellar degeneration, low-frequency rTMS over multiple areas of the cerebellum has been reported to be beneficial [2,6]. The improvement in coordination in these patients is thought to be the result of reduction in the inhibitory signals from Purkinje cells and dentate nucleus, enhancing the activation of the motor cortex and vestibular nuclei [4]. Intermittent theta burst stimulation (iTBS), an excitatory TMS protocol, was found to result in clinical improvement in cerebellar stroke patients with ataxia when applied over the damaged lateral cerebellum [7]. Even though the effects of different frequencies of TMS over the cerebellum are not fully understood, the present report further suggests the beneficial effects of high-frequency cerebellar rTMS in patients with SCA6. The application of high-frequency rTMS over the middle cerebellum can potentially provide a safe, non-invasive, easily tolerated treatment option for patients with SCA6, which we believe merits further exploration in larger patient population studies.

Author contributions

Ge Dang contributed to manuscript drafting and revising, data analysis and picture preparation. Xiaolin Su, Zhifan Zhou and Sixuan Che contributed to manuscript revising, data acquisition and data analysis. Silin Zeng and Siyan Chen contributed to manuscript revising and data analysis. Yi Guo contributed to study design, manuscript revising, data analysis and study supervision.

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Disclosure

The authors report no disclosures.

Conflicts of interest

The authors declare no competing financial interests.

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