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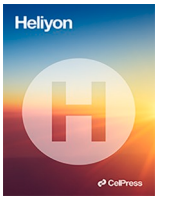

Case report

Efficacy of high-frequency repetitive transcranial magnetic stimulation in a family with spinocerebellar ataxia type 3: A case report

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ABSTRACT

Introduction: Spinocerebellar ataxia type 3 (SCA3) is a common autosomal dominant hereditary ataxia, which is caused by a cytosine-adenine-guanine (CAG) repeat expansion on the causative gene ATXN3, usually with lower extremity ataxia as the first symptom, and effective treatment is scarce. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique that regulates the cerebellum and the neural network connected to it.

Methods: Herein, we report familial cases of SCA3 in two nephews and their aunt, each of whom was treated with high-frequency (5 Hz) rTMS. The rTMS treatment lasted 2 weeks, once daily for 5 consecutive days a week, about 20 minutes each session. The Scale for the Assessment and Rating of Ataxia (SARA), the International Cooperative Ataxia Rating Scale (ICARS), and proton magnetic resonance spectroscopy (^{1}H-MRS) examination were evaluated before and after rTMS treatment.

Results: We found that the ICARS scores improved significantly ($p = 0.04$), and the NAA/Cr values were elevated in vermis and both cerebellar hemispheres after rTMS treatment.

Conclusion: Our study suggested that high-frequency rTMS therapy can contribute to the improvement of cerebellar NAA/Cr value of SCA3 patients, and improve posture and gait as well as limb kinetic function in SCA3 patients.

1. Introduction

Spinocerebellar ataxia type 3 (SCA3) is an autosomal dominant hereditary neurodegenerative disorder, caused by an abnormal expansion of cytosine-adenine-guanine (CAG) present in the ATXN3 gene, loss or degeneration of Purkinje cells in cerebellum is an important pathological change [1]. SCA3 was first recognized in several families of Azorean descent as a heritable "ataxia-plus" disorder. The genetic mutation causing SCA3 was mapped to chromosome 14q32.1 by two separate groups: one group studying the Azorean-linked lineages and another European group which had designated the disease SCA3 after discovering that the genetic locus in families exhibiting similar symptoms to SCA1 and SCA2 was distinct from these two previously identified diseases [2]. Patients with

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SCA often present with motor symptoms, including deficits to the control of standing posture and gait. These deficits greatly increase the risk of falling and losing functional independence [3]. Normally, the cerebellum regulates the standing posture and gait through the cerebello-thalamo-cortical (CTC) pathway [4]. The autopsy of the SCA3 patient showed moderate neuronal loss and gliosis in the dentate nucleus and Purkinje cell layer of cerebellum [5]. The degeneration or loss of Purkinje cells reduces the regulatory role of the CTC pathway [4]. So far, there is no effective therapy for SCA3.

High-frequency rTMS can improve the excitability of nerve cells, and several studies have confirmed the safety of high-frequency rTMS [6,7]. We hypothesized that high-frequency rTMS could improve the excitability of Purkinje cells, and thus improve the patients' symptoms. In this study, we report familial cases of SCA3 in two nephews and their aunt, each of whom was treated with high-frequency (5Hz) rTMS.

2. Case report

Case 1 is a 55-year-old woman with a 21-year history of gait instability, initially with difficulty in running and climbing stairs. She visited our hospital with complaints of severe postural instability and difficulty walking. Nerve conduction studies (NCS) revealed multiple peripheral neuropathy. Case 2 (nephew of case 1) is a 36-year-old man with an 8-year history of gait instability. Case3 (nephew of case 1) is a 48-year-old man with a 23-year history of gait instability. The number of CAG repeats of the ATXN3 gene was shown in Fig. 1A. The clinical features of these patients were detailed in supplementary material 1.

3. Methods

This study was approved by the ethics committee of the Affiliated Hospital of Hangzhou Normal University. All subjects participated voluntarily and signed informed consent. The high-frequency rTMS therapy was performed using S-100 (YINGCHI, SHENZHEN, GUANGDONG, CN). A figure-8 coil was placed above the inion and both cerebellar hemispheres (4 cm to the right of inion and 4 cm to the left of the inion). All patients received 10 sessions of rTMS intervention, conducted once daily for 5 consecutive days a week for 2 weeks, about 20 minutes of 5Hz rTMS stimulation each session. The ataxia severity was assessed by one doctor using the International Cooperative Ataxia Rating Scale (ICARS) and the Scale for the Assessment and Rating of Ataxia (SARA) before (day 0) and after (day 12) the rTMS treatment. In addition, the value of N-acetyl aspartate (NAA)/creatine (Cr) and choline complex (Cho)/Cr in the vermis and cerebellar hemispheres were detected by a proton magnetic resonance spectroscopy (^{1}H-MRS), using a 3.0-T GE Discovery MR-750 before (day 0) and after (day 12) the rTMS treatment (The protocols of spectroscopy were detailed in the supplementary material 2.).

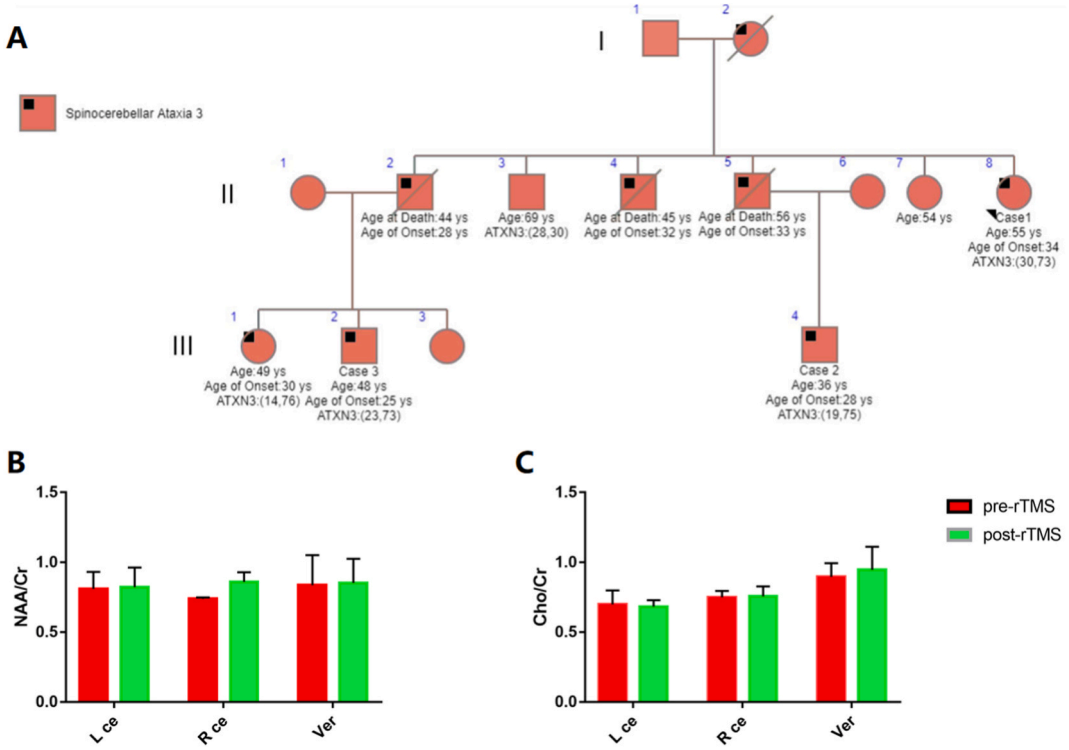

Fig. 1. The pedigree diagram of the patients (Squares represent men, circles represent women) (A), changes in the values of NAA/Cr (B), and Cho/Cr (C) in the cerebellar vermis, left and right cerebellar hemisphere before and after high-frequency rTMS therapy. L ce: left cerebellar hemisphere; R ce: right cerebellar hemisphere; Ver: cerebellar vermis.

4. Results

After 10 sessions, there was a significant improvement in the ICARS score (pre-rTMS vs. post-rTMS = 38.67 ± 16.17 vs. 34.33 ± 15.95, $p = 0.04$) with paired *t*-test, the score improved mainly in the sub-scale of postural and gait, as well as sub-scale of kinetic function (Table 1). The SARA scores in case 1 was improved dominantly (pre-rTMS vs post-rTMS: 23 vs 17) (Table 1). The NAA/Cr values in the vermis, left and right cerebellar hemispheres were elevated compared to those before rTMS treatment (Fig. 1B), but the Cho/Cr values were comparable before and after rTMS treatment (Fig. 1C).

5. Discussion

In this study, three SCA3 patients were treated with high-frequency rTMS for 10 sessions, and we found improvements in both ICARS score and NAA/Cr value after rTMS intervention. The ICARS and the SARA were developed as reliable and valid rating scales of ataxia. Compared to baseline (before rTMS), rTMS improved mainly performance within the "postural and gait" sub-scale and the "limb kinetic function" sub-scale of ICARS score. The SARA scores were comparable before and after rTMS treatment. The reasons for the improvement of ICARS score after rTMS treatment, while the improvement of SARA score was not obvious are as follows: First, compared with SARA, the ICARS scale has a more detailed assessment of motor function and a larger score, thus, the score changes caused by ataxia are magnified in ICARS; Second, the patients had an earlier age of onset and a longer duration of disease in our study, and it would be difficult to improve in that condition; the sessions might be not enough. The age of onset is 28.33 ± 5.51 years, and disease duration is 17.33 ± 8.14 years in our study, which indirectly indicates that the disease progresses to a severe state and the response to rTMS intervention would decrease. Several rTMS studies with significant improvements were conducted with 20 sessions instead of 10 sessions [3,6]. Therefore, it is reasonable to increase the number of sessions to 20 in future studies, although this may reduce patient compliance.

In ^{1}H-MRS, the resonance peak of each metabolite present in biological tissues shows a characteristic pattern at very specific resonance frequencies, which allows for the in vivo quantification of the concentration of various metabolites [8]. NAA is an indicator of neuronal viability and integrity, and Cho is an indicator of membrane metabolism, Cr is associated with brain energy metabolism, served as a reference for comparisons [9]. rTMS can increase the regional cerebral blood flow (rCBF), thereby improving neuronal energy metabolism [10,11], which can improve regional NAA value. In this study, MRS showed that NAA/Cr values were elevated after rTMS treatment in the cerebellum, especially in the cerebellar hemispheres. This improvement of NAA/Cr values corresponded well with the improvement in the "postural and gait" sub-scale and the "limb kinetic function" sub-scale of ICARS score. The Cho/Cr values were comparable before and after rTMS treatment. This may be due to the following reasons: First, the Cho/Cr value in the cerebellum of SCA3 patients was only mildly decreased compared with normal [9]; Second, the sessions may be not enough as mentioned above.

6. Conclusion

In summary, our study suggested that high-frequency rTMS therapy can contribute to the improvement of cerebellar NAA/Cr value of SCA3 patients, and improve posture and gait as well as limb kinetic function in SCA3 patients.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

Table 1
The comparison of scores of ICARS and SARA before and after high-frequency rTMS therapy.

	Pre-rTMS			Post-rTMS		
	case1	case2	case3	case1	case2	case3
ICARS	56/100	24/100	36/100	52/100	21/100	30/100
Posture and gait	30/34	9/34	12/34	28/34	7/34	10/34
Kinetic function	20/52	11/52	18/52	17/52	10/52	14/52
Speech disturbance	4/8	2/8	4/8	5/8	2/8	4/8
Oculomotor dysfunction	2/6	2/6	2/6	2/6	2/6	2/6
SARA	23/40	9/40	13/40	17/40	9.5/40	13.5/40
Gait	6/8	2/8	2/8	6/8	2/8	3/8
Stance	6/6	2/6	2/6	5/6	2/6	2/6
Sitting	2/4	0/4	0/4	0/4	0/4	1/4
Speech disturbance	3/6	2/6	3/6	3/6	2/6	3/6
Finger chase	2/4	0/4	0/4	0/4	0/4	0/4
Nose-finger test	1/4	1/4	1.5/4	1/4	0.5/4	1/4
Fast alternative hand movement	1/4	1/4	1.5/4	1/4	0.5/4	0.5/4
Heel-shin slide	2/4	1/4	3/4	1/4	2.5/4	3/4

The ICARS includes posture and gait, kinetic function, speech disturbances, oculomotor dysfunction; the SARA includes gait, stance, sitting, speech disturbance, finger chase, nose-finger test, fast alternative hand movement, heel-shin slide.

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.heliyon.2023.e16190.

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