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Therapeutic Efficacy of Transcranial Magnetic Stimulation for Hereditary Spinocerebellar Degeneration

Hiroshi Shimizu, Takehide Tsuda, Yusei Shiga, Kohichi Miyazawa, Yoshiaki Onodera, Michiko Matsuzaki, Ichiro Nakashima, Katsutoshi Furukawa, Masashi Aoki, Hiroyuki Kato, Tetsuro Yamazaki[1] and Yasuto Itoyama

Department of Neurology and [1]Department of Radiology, Tohoku University School of Medicine, Sendai 980-8574

Shimizu, H., Tsuda, T., Shiga, Y., Miyazawa, K., Onodera, Y., Matsuzaki, M., Nakashima, I., Furukawa, K., Aoki, M., Kato, H., Yamazaki, T. and Itoyama, Y. *Therapeutic Efficacy of Transcranial Magnetic Stimulation for Hereditary Spinocerebellar Degeneration.* Tohoku J. Exp. Med., 1999, **189** (3), 203-211 —— We applied transcranial magnetic stimulation (TMS) as a therapeutic approach for patients with spinocerebellar degeneration (SCD). The subjects were four familial SCD patients (three men and one woman) aged from 27 to 76 years old. They were genetically analysed as two spinocerebellar ataxia type 6 (SCA 6), one SCA 1, and one SCA 7. The durations of their illness ranged from 1 to 7 years. Ten consective magnetic pulses were delivered over the scalp corresponding to the right cerebellar hemisphere, the middle of the cerebellum and the left cerebellar hemisphere, respectively, every day for 21 days. In all patients, the time and the number of steps required for a 10 m walk examination were significantly decreased after TMS trial compared with those before TMS. The number of feasible steps in tandem gait test increased. The total length of tracing body balance for 30 seconds measured by gravinometer was significantly decreased. However, nystagmus, dysarthria or incoordination of the upper limbs did not change after TMS trial. It is of interest that the blood flow of the cerebellar hemisphere, putamen and pons were significantly increased during the TMS trial. Although we do not know the exact mechanism by which TMS improved the ataxic gait, we speculate the increase of blood flow in the cerebellum, putamen and pons takes part in the improvement. These findings suggest that TMS over the cerebellum may be an effective therapy for patients with SCD. ——— transcranial magnetic stimulation; therapeutic magnetic stimulation; cerebellar blood flow; spinocerebellar degeneration; ataxic gait

Hereditary spinocerebellar degeneration (SCD) is a clinically and neuropath-

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Address for reprints: Takehide Tsuda, M.D., Ph.D., Department of Neurology, Tohoku University School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan.
e-mail: ttsuda@nn.iij4u.or.jp

ologically heterogenous neurologic disorder with a dysfunction of the cerebellum and related systems (Adams et al. 1997). Recently, there have been considerable advances in the diagnosis of familial SCD by using gene analysis techniques. Nowadays, seven kinds of hereditary spinocerebellar ataxia (SCA) have been genetically identified, such as SCA 1, 2, SCA 3/ Machado-Joseph disease, SCA 6, 7, 8 or dentato-rubro-pallido-luysian atrophy. However, no therapeutic approach for SCD have been found in these ten years.

Transcranial magnetic stimulation (TMS) was originally developed for evaluating motor functions in the central nervous system (Barker et al. 1985). However, it has recently been applied for therapeutic purpose, and several studies have suggested clinical effects for depression (George et al. 1995), Parkinson's disease (Mally and Stone 1999) and epilepsy (Tergau et al. 1999). In our trial of TMS in normal subjects, TMS over the unilateral motor cortex increased glucose metabolism and blood flow in the ipsilateral premotor cortex and contralateral cerebellar hemisphere (Shimizu et al. in press). Since the blood flow is decreased in the cerebellum of some SCD patients, we applied TMS for hereditary SCD patients.

Materials and Methods

Patients

Four patients with hereditary SCD were enrolled in this study. None of the patient had a previous history of seizure or cardiac diseases.

Electroencephalography (EEG) of all patients showed no paroxysmal discharges. We received written informed consent from all four patients prior to this study. The ethics committee of Tohoku University approved this study.

Patient 1 was a 62-year-old male, genetically diagnosed as having SCA 6. An uncle and an elder sister had allied disorders. He noticed unsteadiness of gait five years previously. Three months later, dysarthria followed, and both symptoms gradually progressed. On admission, neurological examination revealed mild dysarthria, gaze-evoked horizontal nystagmus, truncal ataxia and limb ataxia. Deep tendon reflexes were generally normal and no pyramidal tract signs were shown. Laboratory findings of the blood and cerebrospinal fluid were within normal limits. Magnetic Resonance Imaging (MRI) showed atrophic changes of the anterior vermis and hemisphere of the cerellum and the supracerebellar cistern was enlarged. Aditionally, he had some lacunar infarctions in the right frontal lobe and putamen (Fig. 1A).

Patient 2 was a 27-year-old male with a diagnosis of SCA 7. He noticed unsteadiness of gait seven years previously. Then, he noticed visual disturbance, dysarthria and difficulty in writing two years latter. These symptoms gradually progressed. An aunt and a grandmother also had SCA 7. On admission, neurological and ophthalmological examinations revealed mild dysarthria, reduced visual acuity and retinal pigmentation bilaterally, truncal ataxia and limb ataxia.

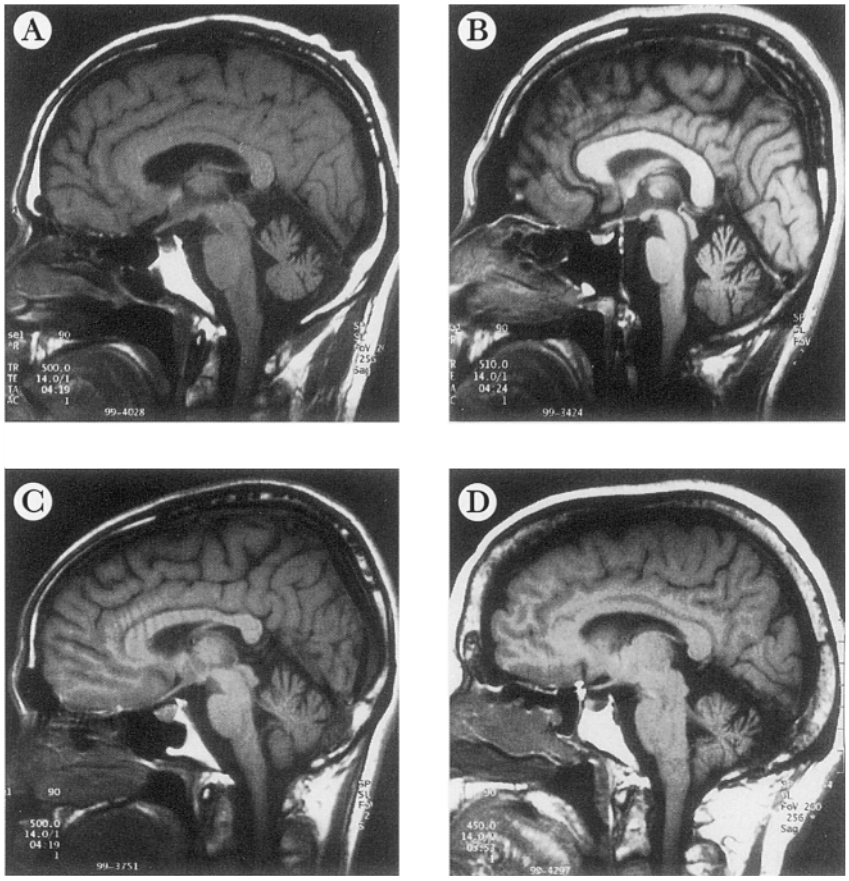

Fig. 1. T1 weighted Magnetic Resonance Imaging of sagital section from four spinocerebellar degeneration patients. A, Patient 1; B, Patient 2; C, Patient 3; D, Patient 4. In patient 1, 3 and 4, the atrophic changes were restricted to the cerebellum. Whereas, patient 2 showed atrophic changes of not only the cerebellum but also the brainstem.

Deep tendon reflexes were generally exaggerated and Babinski signs were presented bilaterally. Laboratory findings of the blood and cerebrospinal fluid were within normal limits. MRI showed moderate atrophic changes of the hemisphere of the cerebellum, and showed mild atrophic changes of the brainstem and midbrain (Fig. 1B).

Patient 3 was a 32-year-old male, genetically diagnosed as SCA 1. He noticed unsteadiness of gait and dysarthria one year before. These symptoms gradually progressed. His father also had SCA 1. On admission, neurological examination revealed mild dysarthria, gaze-evoked horizontal nystagmus and truncal ataxia. Deep tendon reflexes were generally exaggerated and Babinski signs were positive. Laboratory findings of the blood and cerebrospinal fluid were within normal limits. MRI showed atrophic changes of the anterior vermis and hemisphere of the cerebellum. However, the brainstem and spinal cord appeared to be normal (Fig. 1C).

Patient 4 was a 76-year-old female, genetically diagnosed as SCA 6. She noticed unsteadiness of gait and dysarthria two years before. Then, her symptoms slowly progressed. Her son was an asymptomatic carrier of SCA 6. On

admission, neurological examination revealed mild dysarthria, slight horizontal and mild vertical nystagmus, truncal ataxia and limb ataxia. Deep tendon reflexes were normal. Laboratory findings of the blood and cerebrospinal fluid were within normal limits. MRI showed moderate atrophic changes of the anterior vermis and hemisphere of the cerebellum, and an old subdural hematoma on the right frontal lobe (Fig. 1D).

TMS over the cerebellum

In these patients, the procedure of TMS was carried out according to the safety guidelines of the International Federation of Clinical Neurophysiology Committee (Rossini et al. 1994) and Japan Society of Electroencephalography and Electromyography, 1994 (The committee on magnetic stimulation in Japan 1994). Intravenous administration of thyrotropine releasing hormone was discontinued more than two weeks before TMS. As TMS with a stimulus strength of below 2.3 Tesla and with an inter-stimulus interval of more than 5 seconds is generally accepted by the Japan Society of Electroencephalography and Electromyography, we followed the safety recommendations. In the present study, we used a Magstim 200 (Magstim, Wales, UK) with a 9 cm circular coil as the transcranial magnetic stimulator. Patients were asked to sit on a chair in a relaxed manner with eyes closed. Ten consecutive pulses were delivered on each lesion. The inter-pulse interval was more than 5 seconds and the duration of the stimulus pulse was 0.1 milliseconds. The stimulator output was adjusted to 100% of maximal output (the mean magnetic field was approximately 1.5 T). We gave TMS over the cerebellum for consecutive 21 days. The stimilus coil was placed tangentially over Iz (international 10–20 system), 4 cm lateral to the right from Iz and 4 cm lateral to the left from Iz.

Clinical and laboratory evaluation

Patients were neurologically examined before TMS and everyday after TMS by two certified neurologists. We also measured the time required and the number of steps during a 10 m walk, and the number of feasible steps on tandem gait. Moreover, we also measured the total length of tracing body balance for 30 seconds using a Gravicometer AS10 (Anima, Tokyo). These parameters were evaluated before and every week during the TMS trial. Each examination was performed three times, then average data were used for the estimation. EEG, Electrocardiography (ECG) and blood examinations were performed before and 21 days after the TMS trial.

We evaluated the cerebellar blood flow by single photon emmision computed tomography using a modified Patlak plot method (Matsuda et al. 1992, 1993) before and three weeks after the TMS trial. ^{99m}Tc-ethyl cysteinate dimer was used as a tracer. We put the regions of interest (ROI) in the bilateral frontal lobes, temporal lobes, occipital lobes, putamens, cerebellar hemispheres and

pontine base. To evaluate blood flow at each region, we calculated the blood flow ratio by dividing the value of a ROI in the cerebellar hemisphere by that of the contralateral frontal lobe. We alao calculated the blood flow ratio by dividing the value of a ROI in each remaining region by that of the ipsilateral frontal lobe. Because the raw data from the frontal lobes were the stablest and unchanged between two trials of each patient. For statistical analysis, paired-t test was used.

Results

All patients tolerated well the three-week TMS trial. In neurological examination after this trial, we did not detect any changes in cognitive functions, extraocular movement and nystagmus, limb ataxia, muscle strength, muscle tonus,

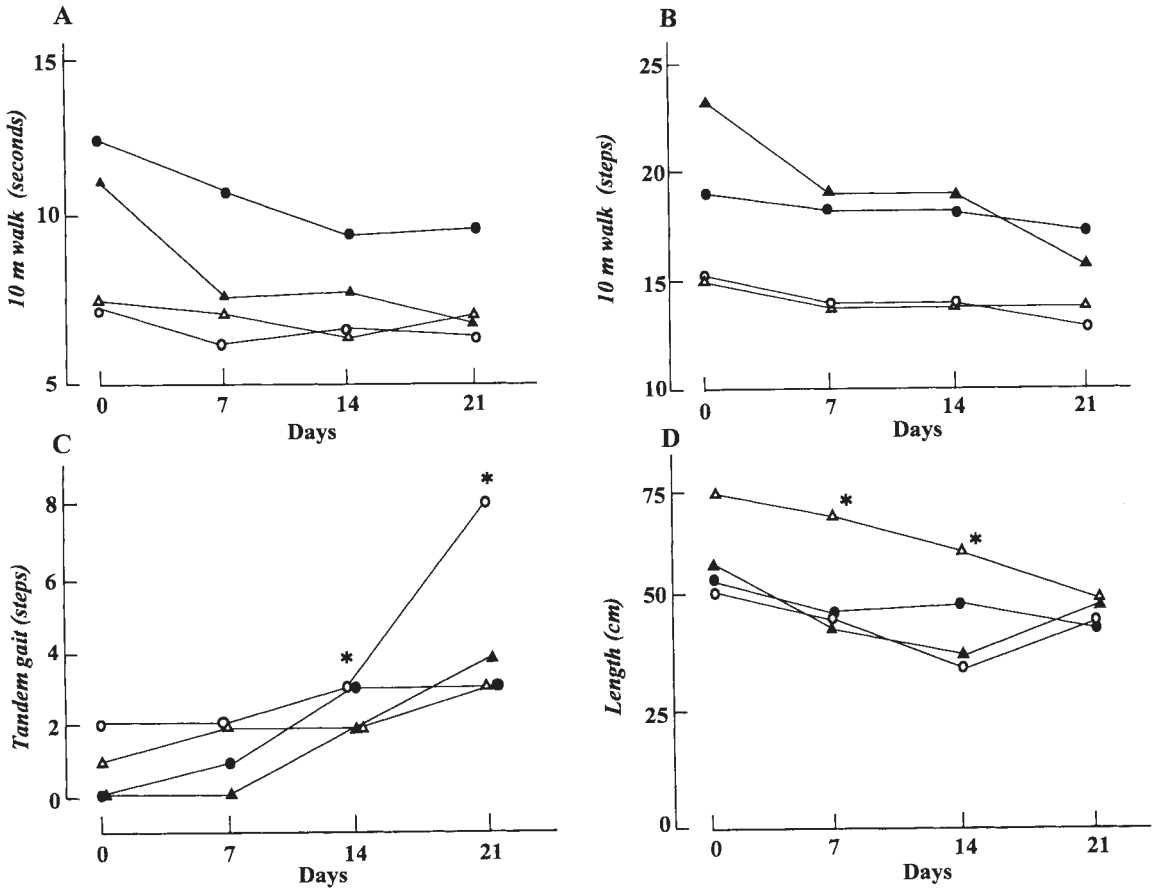

Fig. 2. A, The time required during a 10 m walk. All patients reduced the time after 21 days of transcranial magnetic stimulation (TMS). B, The steps required for a 10 m walk. All patients, especially patient 1, decreased the steps after 21 days of TMS. C, The number of feasible steps in tandem gait. All patients increased the number after 21 days of TMS. In patient 1, the number increased from 0 (before TMS) to four (after 21 days of TMS). $^*p<0.05$. D, The total of length of tracing body balance for 30 seconds standing with eyes open. All patients decreased the length after 21 days of TMS. $^*p<0.05$.
▲, Patient 1; △, Patient 2; ○, Patient 3; ●, Patient 4.

deep tendon reflexes or pathological reflexes. In general, all the patients improved on gait subjectively as well as objectively from the first or second week after TMS.

A reduction of the time required during a 10 m walk was observed in all patients after the TMS trial. Especially, the reduction was remarkable in patient 1 and 4 (Fig. 2A). All patients slightly decreased the number of steps during the 10 m walk, and an especially remarkable change was observed in patient 1 (Fig. 2B). The number of feasible steps in tandem gait was increased in all the patients. In case of patients 1 and 4, it was impossible to perform tandem gait before TMS. However, they were able to walk several steps on the tandem gait test after TMS (Fig. 2C). The total length of the tracing body balance for 30 seconds standing measured by gravinometer was significantly shortened in all patients. Especially, case 2 was remarkably, shortened (Fig. 2D). The blood flow in the bilateral cerebellar hemispheres, putamens and pontine base were significantly increased compared to those of before TMS ($p<0.005$, $p<0.005$ and

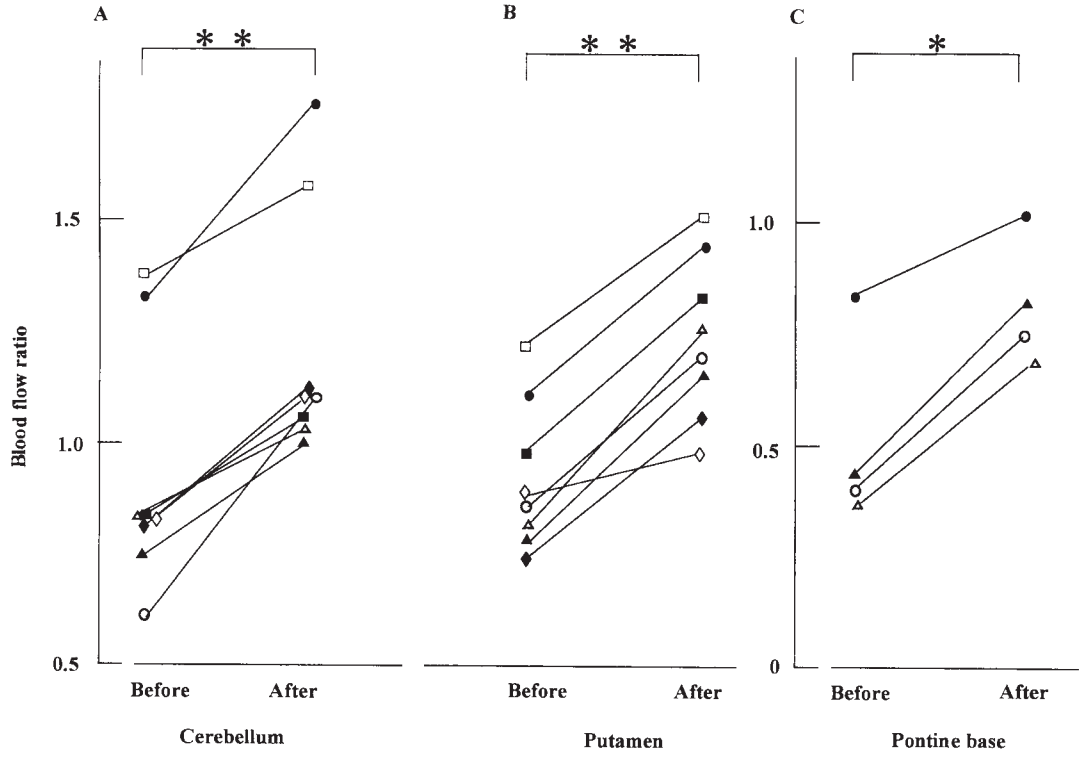

Fig. 3. The blood flow ratio.
A, The ratio of blood flow between the contralateral frontal lobe and cerebellar hemisphere. B, The ratio of blood flow between the ipsilateral frontal lobe and putamen.
Patient 1: ◆, R; ▲, L. Patient 2: ■, R; △, L. Patient 3: ◇, R; ○, L. Patient 4: □, R; ●, L.
C, The ratio of blood flow between the ipsilateral frontal lobe and pontine base. All patients showed an increase in the blood flow ratio.
$^{*}p<0.05$. $^{**}p<0.01$.
▲, Patient 1; △, Patient 2; ○, Patient 3; ●, Patient 4.

$p<0.05$, respectively) (Figs. 3A-C). We did not detect any adverse effects during the three-week TMS trial. The EEG, ECG and blood examinations showed no abnormal findings three weeks after TMS.

Based on these neurological examination, findings and several other parameters, we think an improvement of the truncal ataxia produced the improvement of ataxic gait.

Discusshon

In the present study, we first applied TMS for therapeutic use in patients with SCD. Our results showed that TMS over the cerebellum significantly improved ataxic gait in four SCD patients. Especially, it is of interest that the impairement of tandem gait, which is a sensitive index of truncal ataxia, was obviously improved. The objective assessment scores for truncal ataxia were consistent with the improvement of the clinical disabilities. It is also noteworthy that TMS treatment was well tolerated and no adversive effects were observed. After three-week TMS trial some patients described a subjective improvement of speech, but we have to be careful when estimating this effect without a reliable estimation of speed. Although TMS was introduced as a diagnostic device for the neurogenic and neuropathological fields more than 10 years before (Barker et al. 1985), only recently have there been some studies showing therapeutic effects of TMS for some neurologic and psychiatric diseases, such as Parkinson disease (Shimamoto et al. 1989; Pascual-Leone et al. 1994; Mally and Stone 1999), depression (George et al. 1995; Reid et al. 1998), intractable epilepsy (Tergau et al. 1999) and neurological bladder (Lin et al. 1997). At this point, the present success in improving gait and body balance in hereditary SCD suggests the possibility that TMS may be a useful tool for the therapy of other types of SCD.

The mechanism by which TMS improved the ataxic gait and truncal ataxia is unclear. TMS was first applied as a therapeutic tool for depression in 1995 by George et al. (1995) and showed some effects. They thought TMS might change β-adrenergic and 5-HT2 receptor characteristics in the patients (Ben-Shachar et al. 1999). TMS also showed clinical effects for Parkinson's disease (Pascual-Leone et al. 1994; Mally and Stone 1999). The mechanisms of its effect are thought to result from changes in the brain monoamine levels (Ben-Shafer et al. 1999; Mally and Stone 1999). Based on these reports, alterations in the neurotransmitters might have been induced by TMS over the cerebellum in our trial.

Moreover, we should pay attention to the increase in blood flow in the cerebellum and other regions after TMS. There have been some reports that TMS increased the blood flow and glucose metabolism of stimulated and associated regions in normal subjects (Siebner et al. 1998; Shimizu et al. 1999). Since we sometimes noticed a decrease in the cerebellar blood flow in patients with SCD and related disorders, we speculate that cerebellar blood flow may relate to the cerebellar function in these disorders. In this study, TMS over the cerebellum

increased the cerebellar blood flow in the SCD patients, which may have played a part in the functional activation of the cerebellum. We need further investigations to verify the mechanisms of TMS for SCD using more patients with several types of SCD.

In conclusion, we showed that TMS over the cerebellum effectively improved ataxic gait in four patients with hereditary SCD without any adverse effects, suggesting the potential of TMS as an alternative therapeutic tool for SCD.

Acknowledgments

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