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Therapeutic benefit of repetitive transcranial magnetic stimulation for severe mirror movements

A case report☆

Han Sun Kim[1], Sung Ho Jang[1], Zee-Ihn Lee[2], Mi Young Lee[3], Yun Woo Cho[1], Migyoung Kweon[4], Su Min Son[1]

1 *Department of Physical Medicine and Rehabilitation, College of Medicine, Yeungnam University, Daegu 705-717, Republic of Korea*
2 *Department of Pediatrics, College of Medicine, Yeungnam University, Daegu 705-717, Republic of Korea*
3 *Department of Physical Medicine and Rehabilitation, Daegu Fatima Hospital, Daegu 701-600, Republic of Korea*
4 *Department of Physical therapy, College of Health and Therapy, Daegu Haany University, Gyeongsan 712-751 Republic of Korea*

Abstract
Congenital mirror movements retard typical hand functions, but no definite therapeutic modality is available to treat such movements. We report an 8-year-old boy with severe mirror movements of both hands. His mirror movements were assessed using the Woods and Teuber grading scale and his fine motor skills were also evaluated by the Purdue Pegboard Test. A 2-week regimen of repetitive transcranial magnetic stimulation produced markedly diminished mirror movement symptoms and increased the fine motor skills of both hands. Two weeks after the completion of the regimen, mirror movement grades had improved from grade 4 to 1 in both hands and the Purdue Pegboard Test results of the right and left hands also improved from 12 to 14 or 13. These improvements were maintained for 1 month after the 2-week repetitive transcranial magnetic stimulation regimen. After 18 months, the mirror movement grade was maintained and the Purdue Pegboard test score had improved to 15 for the right hand while the left hand score was maintained at 13. This occurred without any additional repetitive transcranial magnetic stimulation or other treatment. These findings suggest that repetitive transcranial magnetic stimulation for this patient had a therapeutic and long-term effect on mirror movements.

Key Words
neural regeneration; neurorehabilitation; clinical practice; mirror movements; Purdue Pegboard test; hand; transcranial magnetic stimulation; hand function; cortex suppression; corticospinal tract; grants-supported paper; neuroregeneration

Research Highlights
(1) The patient in this study showed severe mirror movements of both hands and impaired function of fine motor coordination.
(2) After 2 weeks of repetitive transcranial magnetic stimulation treatment, the patient showed dramatic improvement of the motor skills of both hands.
(3) After 18 months of repetitive transcranial magnetic stimulation treatment, his mirror grade was maintained without additional repetitive transcranial magnetic stimulation or rehabilitative treatments.
(4) Repetitive transcranial magnetic stimulation treatment likely has a therapeutic and long-term effect on mirror movements.

Han Sun Kim☆, M.D.

Corresponding author: Su Min Son, M.D., Department of Physical Medicine and Rehabilitation, College of Medicine, Yeungnam University, 317-1, Daemyungdong, Namku, Daegu 705-717, Republic of Korea, sumin430@hanmail.net.

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INTRODUCTION

The term mirror movement refers to involuntary and unnecessary movements of the contralateral side during voluntary movements on one side of the symmetrical body part[1]. The mechanism responsible for mirror movements is unclear. Previous studies have demonstrated that mirror movements may be mediated by the fast-conducting corticospinal pathways which can connect abnormally to the hand area of only one primary motor cortex or connect to a separate ipsilateral corticospinal projection[2-3]. Mirror movements have been described in various neurological conditions, including cerebral palsy, cerebrovascular disease, Parkinson's disease, and Friedreich's ataxia[2-3]. Persistent congenital mirror movements are characterized by ipsilateral fast-conducting corticospinal projections and bilateral primary motor cortex output after intended unimanual hand contraction[1-2]. Persistent congenital mirror movements of the hands hinder the activities of daily life and adversely influence the development of fine motor skills, especially in children[4]. However, no definite treatment modality is available for congenital mirror movements. A recent study has shown that modulations of the intensity or velocity of movements can reduce mirror movements and that it is not possible to control all movements in daily life[4].

Repetitive transcranial magnetic stimulation provides a safe and non-invasive technique for brain stimulation[5]. In 2008, Kirton *et al* [6] demonstrated the safety and feasibility of repetitive transcranial magnetic stimulation treatment in pediatric patients with subcortical stroke. Repetitive transcranial magnetic stimulation can modulate local neural activities in the brain and facilitate functional reorganization, and consequently may affect clinical symptoms in various neurological conditions characterized by altered motor cortex function[7]. Repetitive transcranial magnetic stimulation is used for various purposes such as enhancing motor recovery, improving depression, relieving neuropathic pain, controlling tremors, and treating dysphagia or spasticity[8-9]. In the current study, we reported dramatic improvement of congenital mirror movements and impaired fine motor skills in a pediatric patient after repetitive transcranial magnetic stimulation treatment.

CASE REPORT

An 8-year-old boy with severe mirror movements and impaired fine motor skills of both hands was treated. The patient had no specific perinatal event. He was born at 39 weeks + 4 days of gestational age and with birth weight of 3.2 kg. There were no definite abnormal signs such as prolonged rupture of membranes, asphyxia, pneumothorax or heart problem. There was no family history of mirror movements or neurological abnormality. His parents informed us that he had no definite sign of abnormal development, such as asymmetry or hand dominance at an early age (< 18 months), and no significant developmental delay. However, they pointed out that the patient suffered from manipulative inabilities, such as the handling of chopsticks and the use of a pencil, due to severe mirror movements. The patient had not been tested or treated for congenital mirror movements by any rehabilitative occupational or physical therapist. The patient's parents provided informed consent for his participation in this study.

MRI was performed during the first visit to determine the presence of any specific brain lesion. A pediatric neuroradiologist found no evidence of abnormal signal intensity. In addition, a physical evaluation by a pediatric neurologist revealed no definite abnormal pattern, such as weakness, asymmetric tone, pathologic reflex, or spasticity, although it was noted that his fine motor coordination was clumsy. His developmental milestones for language, examined by a speech therapist, were within normal range in both receptive and expressive language skills. Cognitive evaluation using the Korean Kaufman Assessment Battery for Children by a clinical neuropsychologist revealed an intelligence quotient of 102, in the normal range[10]. Mirror movements were evaluated using the Woods and Teuber grading scale[11] by two pediatric neurologists blinded to experimental design. Involuntary mirror movements of one hand during grip-release by the other were graded using a 0–5 scale: 0 = no clear imitative movement of contralateral homologous regions; 1 = very mild mirror movement or increased tone; 2 = slight but unsustained repetitive movement; 3 = briefer repetitive movement, less than one half the range of motion of the metacarpophalangeal joint in the contralateral hand; 4 = stronger repetitive movement, of more than half the range of motion of the metacarpophalangeal joint in the contralateral hand; 5 = movement equal to that of the expected range of motion of the intended hand.

At the first visit, the patient displayed strong repetitive movements in both hands, that is, of more than half the range of motion of the metacarpophalangeal joint in the contralateral hand, and was awarded grade 4 on the mirror movement scale by both of the two blinded observers. The Purdue Pegboard Test[12] was conducted to measure hand function and to evaluate fine motor skills, including speed and dexterity. A pediatric occupational therapist evaluated the patient's performance on the Purdue Pegboard Test. The test consists of two parts: (1) Right Hand. Subjects insert small pins into holes on the board using only their right hand. The number of pins successfully placed in the holes for 30 seconds is counted. (2) Left Hand. Subjects insert small pins into holes, now using only their left hand. Again, they were timed for 30 seconds and the pins are counted. The normative data for 8-year-old normal children suggest that the average score range is 12.07 to 13.90[13]. The patient showed a Purdue Pegboard Test score of 12 for both hands.

Repetitive transcranial magnetic stimulation was conducted to treat the mirror movements because the patient's parents refused any other rehabilitative therapy for personal reasons. The parents found it difficult to attend scheduled daily therapeutic sessions because of his school schedule and refused therapy of duration greater than 2 weeks. The potential side effects of repetitive transcranial magnetic stimulation therapy, which include headache, negative cognitive affect, and seizure, were explained to the parents. Transcranial magnetic stimulation was performed with an angled large figure-of-eight coil (angle 120°, diameter 80 mm, DB-80, MagPro. Co., Ltd., Hertfordshire, UK) and was conducted by an expert with more than 8 years of repetitive transcranial magnetic stimulation experience.

Motor evoked potentials were recorded using surface electrodes and a Dantec Counterpoint Electromyography machine (Dantec, Skovlunde, Denmark). The point of intersection between the midsagittal line that connects the nasion and inion and the interaural line was designated Cz and assigned the coordinates (0, 0). The interaural line was designated the *X* axis and midsagittal line the *Y* axis, which meant that points lying to the right and in front of Cz were positive, and points lying to the left of and behind Cz were negative. Stimulation was conducted to identify the location of the hot spot for motor evoked potentials in the ipsilateral abductor pollicis brevis, which represents a mirror movement hot spot[14]. Since the patient was right handed, repetitive transcranial magnetic stimulation was performed at the right primary motor cortex to induce ipsilateral corticospinal tract inhibition. The hot spot for the ipsilateral abductor pollicis brevis was stimulated, and the motor threshold was defined as the minimum transcranial magnetic stimulation intensity necessary to induce a motor evoked potential exceeding 50 μV for more than half of four trials of stimulations. The site with the lowest excitation threshold, shortest latency, and highest amplitude was designated as the hot spot. Results showed that the hot spot in the subject was at (4, 1), which coincided with the primary motor area identified as a mirror movement hot spot in a previous study[15]. The coil was placed tangentially to the scalp, with the handle pointing 45˚ posterolaterally.

The repetitive transcranial magnetic stimulation protocol adopted to modulate the excitability of the stimulated area was: repetitive transcranial magnetic stimulation at 1 Hz for 15 minutes (a total of 900 pulses) for five sessions a week at a resting motor threshold of 115% for 2 weeks[16]. The patient had repetitive transcranial magnetic stimulation sessions on weekdays from Monday to Friday, once per day. The duration over which the sessions were given was 2 weeks and the total number of sessions was 10. During every repetitive transcranial magnetic stimulation procedure, the patient was monitored by a pediatric neurologist and no definite adverse response occurred during any procedure.

A second evaluation conducted at 1 week after the 2-week treatment regimen revealed that mirror movement grades had improved from grade 4 to grade 1 in both hands (Figure 1A). A second Purdue Pegboard Test for estimating hand function conducted at the same time also indicated improvements: 14 for the right hand and 12 for the left hand (Figure 1B). After repetitive transcranial magnetic stimulation treatment, the patient was able to manipulate chopsticks and write with a pencil. At 1 month after repetitive transcranial magnetic stimulation, the patient maintained a mirror movement grade of 1, although no further repetitive transcranial magnetic stimulation treatments had been given. Furthermore, hand function had markedly improved and a Purdue Pegboard Test conducted at the time showed a score of 14 for the right and 13 for the left. The cognitive evaluations using Korean Kaufman Assessment Battery for Children were performed before and after treatment to check for possible adverse effects such as cognitive deterioration. However, no definite treatment-related change was noted.

At 18 months after repetitive transcranial magnetic stimulation treatment, the patient and his parents revisited our clinic, and, although repetitive transcranial magnetic stimulation treatment had been provided in the interim, the patient had retained a mirror movement grade of 1. The Purdue Pegboard Test score had improved to 15 for the right hand and was maintained at 13 for the left. The ability to use chopsticks and a pencil were maintained.

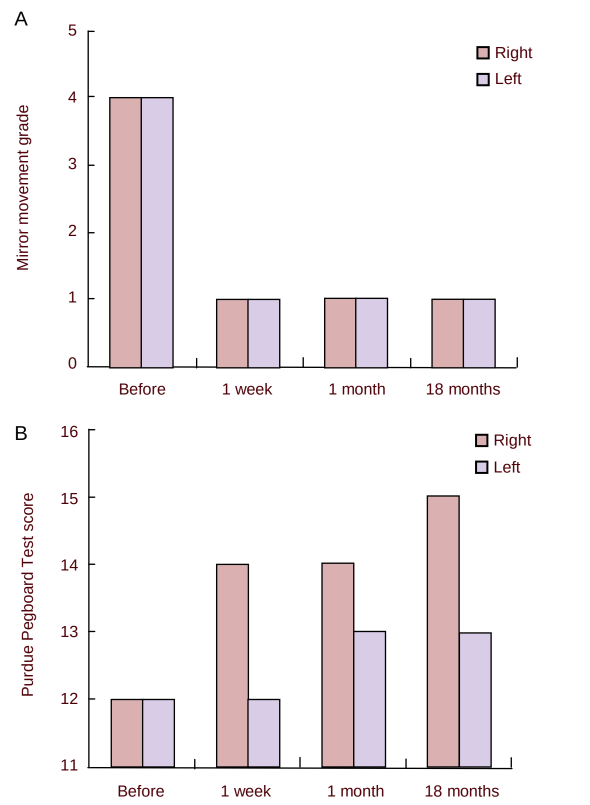

Figure 1 Results of repetitive transcranial magnetic stimulation for the treatment of mirror movements in an 8-year-old boy.

(A) Improvement of mirror movements of both hands assessed by the Woods and Teuber grading scale. (B) Improvement of fine motor skills of both hands assessed by the Purdue Pegboard Test.

The Woods and Teuber grading scale ranges from 0–5, with the lower grades indicating more significant improvement of mirror movements. The normative Purdue Pegboard Test scores for 8-year-old normal children suggest that the average score range is 12.07 to 13.90, with higher scores indicating better motor skills.

DISCUSSION

In the current study, severe mirror movements and fine motor coordination skills showed dramatic improvement after repetitive transcranial magnetic stimulation-induced ipsilateral motor cortex suppression. Furthermore, the therapeutic effect persisted for at least 18 months after repetitive transcranial magnetic stimulation treatment.

Congenital mirror movements are related to the ipsilateral corticospinal tract[1-2] and thus we hypothesized that mirror movements might be improved by inhibiting the activation of the ipsilateral corticospinal tract using repetitive transcranial magnetic stimulation. After 2 weeks of repetitive transcranial magnetic stimulation treatment, mirror movement grades reduced obviously in both hands, which we attribute to the therapeutic effect of repetitive transcranial magnetic stimulation because no other therapy was provided.

We believe that interhemispheric inhibition may have been the basis of this treatment success. Interhemispheric inhibition functions *via* a transcallosal connection. Inhibition of this transcallosal connection begins between the ages of 6 and 10 years, and is usually complete after the age of 10 years (the time of corpus callosum maturation)[17-18]. Interhemispheric inhibition is inversely correlated with mirror activity and transcallosally- mediated interhemispheric inhibition plays an important role in suppressing unwanted mirror movements[19]. Inhibitory repetitive transcranial magnetic stimulation at 1 Hz could be helpful for treating mirror movements[20], but even with this documented optimism, the observed improvement of the left hand mirror movements exceeded our expectations. We suggest that immaturity of the brain of our patient possibly led to a transcallosal connection. That is, repetitive transcranial magnetic stimulation might influence both hemispheres through an immature transcallosal connection in the brain, and thus unilateral inhibition influenced both hands although there existed a difference of improvement patterns between both hands. Since this is a preliminary study of one case, the results cannot be generalized.

However, the observations that repetitive transcranial magnetic stimulation increased right (ipsilateral) hand Purdue Pegboard Test scores and reduced mirror movement grades are consistent with the findings of previous studies on the effect of inhibitory repetitive transcranial magnetic stimulation on ipsilateral primary motor cortex[20-22]. In a previous study that applied repetitive transcranial magnetic stimulation in inhibition mode to the ipsilateral primary motor cortex, contralateral primary motor cortex, and ipsilateral premotor cortex of 16 healthy subjects, it was found that fine motor skills of the ipsilateral hand were improved by repetitive transcranial magnetic stimulation of the ipsilateral primary motor cortex[19]. In another study conducted in 18 healthy adults, it was found that 1 Hz repetitive transcranial magnetic stimulation applied over the left primary motor cortex improved finger movement kinematics, hand tapping, and left hand grasp strength[22].

However, left Purdue Pegboard Test scores, unlike right Purdue Pegboard Test scores, showed no definite immediate repetitive transcranial magnetic stimulation-mediated effect, but at second evaluations conducted 1 month later, left hand Purdue Pegboard Test scores were found to have increased from 12 to 13. These results suggest that mirror movement reductions might facilitate the use of hands in daily life and increase fine motor skills without additional rehabilitative therapy.

It is of interest that the patient had maintained fine motor skills in performing daily activities through 18 months after repetitive transcranial magnetic stimulation without additional repetitive transcranial magnetic stimulation treatment. Furthermore, the right hand Purdue Pegboard Test score had improved from 14 to 15. These results suggest the possibility of long-term effects from repetitive transcranial magnetic stimulation.

Many studies have suggested that repetitive transcranial magnetic stimulation has various adverse effects, such as headaches, spasm, and discomfort in the stimulated area, but no negative effects on general health have been reported[8, 23]. Generally, repetitive transcranial magnetic stimulation is a well-tolerated, relatively safe procedure in adults. Compared with adults, this procedure has certainly not been proven safe for children nor are there safety guidelines in pediatrics. However, there have been no reported major adverse effects such as seizure in most of studies in which repetitive transcranial magnetic stimulation has been performed[24]. In the present study, no definite side effects were observed during or after repetitive transcranial magnetic stimulation treatment sessions.

Taken together, repetitive transcranial magnetic stimulation therapy administered for 2 weeks reduced mirror movements in both hands and markedly improved hand function and this therapeutic effect lasted for at least 18 months. Our observations suggest that repetitive transcranial magnetic stimulation can be a therapeutic modality for congenital mirror movement disorders. However, this is a case report based on experience with a single patient, and it is unclear whether this observation is an epiphenomenon or demonstrates the effectiveness of repetitive transcranial magnetic stimulation treatment. In addition, this study is also limited by the lack of monitoring between 1 month and 18 months after treatment. However, to the best of our knowledge, no previous study has claimed that repetitive transcranial magnetic stimulation has a beneficial effect on congenital mirror movements in pediatric subjects; the authors believe that this result can stimulate an increased interest for researchers and lead to new trials with specific protocols for repetitive transcranial magnetic stimulation treatment in pediatric patients. Larger scale studies which include active treatment and control groups with regular long-term follow-up are warranted to confirm our findings.

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