Journal of Neurology & Neurophysiology
Feiyong J, et al., J Neurol Neurophysiol 2015, 6:3
DOI: 10.4172/2155-9562.1000291

Research Article Open Access

Infra-low Frequency Transcranial Magnetic Stimulation Effectively Improves the Motor Function in Children with Spastic Cerebral Palsy

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Received date: March 17, 2015; **Accepted date:** May 01, 2015; **Published date:** May 05, 2015

Abstract

Background: Cerebral palsy (CP) is one of the major diseases that lead to severe disability and seriously impacts the quality of life of children. Infra-low frequency transcranial magnetic stimulation (ILF-TMS) is a new technique of noninvasive brain stimulation that exactly regulates the power of specific neurotransmitters through a special magnetic field. Our study was in order to investigate the efficacy of ILF-TMS treatment in children with spastic cerebral palsy.

Methods: 113 spastic cerebral palsic children were randomly divided into two groups: conventional rehabilitation group and ILF-TMS treatment group, Healthy control group was established at the same time. In conventional rehabilitaion group, children were treated with conventional rehabilitation treatment; In ILF-TMS treatment group were treated with ILF-TMS in addition to conventional rehabilitation treatment. Neurotransmitter in the brain was recorded with encephalofluctuograph (EFG) before and after ILF-TMS treatment. Gross Motor Function Measure (GMFM), Fine Motor Function Measure (FMFM) and Gesell development scale (GDS) were used to comprehensively evaluate the motor function in children with spastic cerebral palsy.

Results: The results showed that the relative power of γ-aminobutyric acid (GABA) in spastic cerebral palsy was lower than that in healthy controls and was increased significantly after ILF-TMS treatment for 3 months. The relative power of glutamate (Glu) in spastic cerebral palsy was higher than that in healthy controls and was reduced significantly after ILF-TMS treatment for 3 months. After 3 months training period there was significant improvements on the GMFM (dimension B, dimension C and dimension D), FMFM (dimension A and dimension B) and GDS (gross motor DA and gross motor DQ) in the ILF-TMS treatment group when compared to conventional rehabilitation group.

Conclusions: These findings indicate that GMFM is a sensitive indicator to assess the treatment efficacy in children with spastic cerebral palsy and ILF-TMS treatment can improve the motor function through regulating neurotransmitters in brain.

Keywords: Spastic cerebral palsy; Infra-low frequency transcranial magnetic stimulation; γ-aminobutyric acid; Glutamate; Gross motor function measure; Fine motor function measure

Abbreviations

Ach: Acetylcholine; CP: Cerebral Palsy; DA: Dopamine; EFG: Encephalofluctuograph; FMFM: Fine Motor Function Measure; GMFM: Gross Motor Function Measure; GDS: Gesell Development Scale; Glu: Glutamate; 5-HT: 5-Hydroxytryptamine Amine; ILF-TMS: Infra-low Frequency Transcranial Magnetic Stimulation; NE: Norepinephrine; rTMS: Repetitive Transcranial Magnetic Stimulation; GABA: γ-Aminobutyric Acid

Introduction

Cerebral palsy (CP) is defined as a permanent disorder of the development of movement and posture, causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain [1-3].

The motor disorders of cerebral palsy are often accompanied by disturbances of speech disorders, visual, sensation, perception, cognition, communication, and behaviour, by epilepsy and by muscle contraction and deformity of limbs [4-13]. With the development of the perinatology and the improved techniques of neonatal intensive unitthe neonatal mortality is reduced significantly, however, the incidence of CP has a tendency to increasement in recenty years [5,14,15]. CP can be classified as spastic, dyskinetic, ataxic, tonic and atonic types according to clinical characteristics c and spastic type accounts for 70% children with CP [16,17].

CP is one of the major diseases that lead to severe disability and seriously impacts the quality of life of children [7,11,12]. In addition to motor function, the level of intelligence structure is commonly an important factor to influence the quality of life in children with cerebral palsy [9,10,13]. The purpose of cerebral palsy management is not only to ameliorate the body morphology and motor function but also to improve the cognitive ability in patient with CP. Although it is timely and debilitated, conventional rehabilitation treatment remains the mainstay for CP therapy at present [18].

There is an imbalance of excitatory and inhibitory neurotransmitters in the brain of children with CP [19,20]. It has been known that repetitive transcranial magnetic stimulation (rTMS) can modulate cortical excitability by focally stimulating the cortical region and has therapeutic potential in children with dystonia [21–25]. Hummel et al found that an interhemispheric imbalance is evident in children with brain injury, and that rTMS treatment can restore this imbalance [26,27]. Several studies demonstrate that rTMS therapy cam improve the motor function [25-30] and working memroy in patients with stroke [31,32].

Infra-low frequency transcranial magnetic stimulation (ILF-TMS) is a new technique of noninvasive brain stimulation that exactly regulates the power of specific neurotransmitters through a special magnetic field (frequency less than 0.2 Hz, magnetic field intensity: less than 500GZ)[33]. The ILF-TMS maybe more safer than the rTMS due to its low magnetic field intensity [33]. Jianlan Xu et al. have reported that consecutive ILF-TMS treatment can recovery the power of the neurotransmitter in mouse [33]. We hypothesized that ILF-TMS can restore the imbalanced neurotransmitters in the brain and then improve the motor and cognitive ability of children with CP. In this study, spastic cerebral palsic children were randomly divided into two groups: conventional rehabilitation group and ILF-TMS treatment group. Assessmental parameters such as GMFM, FMFM, GDS and EFG have been used to comprehensively evaluate the efficacy of ILF-TMS on intelligence structure and motor function in children with spastic cerebral palsy.

Methods

Participants

A total of 113 spastic cerebral palsic children were recruited from Department of pediatric neurology and rehabilitation, First Hospital of Jilin University from May 2014 to September 2014. They were randomly divided into two groups: conventional rehabilitation group (n=53) and ILF-TMS treatment group (n=60). The healthy control group was established at the same time. Neurotransmitters in the brain were recorded by encephalofluctuograph (EFG) in both children with CP and healthy control before ILF-TMS intervention and then nurotransmitters in the brain were detected repeatedly at timepoints of 1 month and 3 months after ILF-TMS treatment, respectively.

Gross Motor Function measurement (GMFM), Fine Motor Function measurement (FMFM) and Gesell development scale (GDS) were used to comprehensively evaluate the intelligence domains and motor function in children between conventional rehabilitation group and ILF-TMS treatment group. Inclusion criteria for participation in the study included: (1) a diagnosis of spastic cerebral palsy; (2) age between 2 and 4 years; (3) ability to follow simple instructions. Exclusion criteria included: (1) debilitating illness before or during the study; (2) surgical procedure during, or up to one year prior to the study; (3) Botunum toxin injection Or baclofen intrathecal pump during or up to six months prior to the study; and (4) inability to follow commands. All the children and their parents or caregivers provided their written consent for their participation in this study, and this study was approved by the ethic committee of the first hospital of Jilin universtity. The trial registration number is ChiCTR-TRC-14004706.

Method

Children in the conventional rehabilitation group (n=53) were only Trained by conventional rehabilitation treatment (physical therapy, occupational therapy, speech therapy, chinese massage, hyperbaric oxygen and so on; once a day, 30 minutes every time for one item). Children in the ILF-TMS treatment group (n=60) were undergone with both conventional rehabilitation treatment and ILF-TMS treatment (once a day, 30 minutes every time, frequence: less than 0.2 Hz, magnetic field intensity: less than 500GZ). The main treatment parameters: γ-aminobutyric acid (GABA), Glutamate (Glu). Adjuvant treatment parameters: 5-hydroxytryptamine amine (5-HT), acetylcholine (ACh), norepinephrine (NE), and dopamine (DA). Neurotransmitters in the brain were recorded by EFG (Kangli-tech company limited, Shenzhen, China) at timepoints before and after ILF-TMS treatment for 1month and 3 months respectively. According to the result of EFG to set the parameters for treatment, using GMFM, FMFM and GDS to do comprehensive evaluation on the two groups before and after treatment for 1 month and 3 months. The GMFM, FMFM and GDS are reliable tools for assessing the motor function and intelligence structure of children with CP. GMFM is a referenced test developed and validated to examine gross motor function skills in children with cerebral palsy and measure changes as a result of intervention [34]. Evidence of the validity and reliability of the GMFM for use in children with cerebral palsy has been extensively established [35,36]. Fine motor function measurement is an important item that can reflect the level of development of fine motor function in cerebral palsic children. Wei Shi et al reported that the reliability, validity and responsiveness of the FMFM and the fine motor functioning of children with cerebral palsy could be effectively measured using the FMFM scale [37,38]. Gesell developmental scale is an instrument to evaluate the level of infant and toddler mental development though the developmental quotient (DQ) to reflect the mature of the neuromotor integrity and function and to reflect the potential of intellectual development.

Statistical Analysis

The data were expressed as median and range. The difference between groups was analyzed by the Friedman test using the SPSS16.0 software. A two-side P value of <0.05 was considered statistically significant.

Results

The demographic and clinical characteristics of the study participants

To detect the neurotransmitters between spastic cerebral palsyic children and healthy control, 113 spastic cerebral palsic children and 20 healthy controls were recruited in this study. There is a significant difference in gestational age and birth weight between the two groups, other difference about the demographic and clinical characteristics between the spastic cerebral palsic children and health control was not found (Table 1).To determine the effects of ILF-TMS treatment on the intelligence structure and motor function in children with spastic cerebral palsy, 113 spastic cerebral palsic children were randomly divided into two groups: conventional rehabilitation group(n=53) and ILF-TMS treatment group(n=60).There was no significant difference about the demographic and clinical characteristics between the two groups (Table 2).

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Parameters	Spastic cerebral palsic children	Healthy control
Number of Participants	113	23
Age (months)	41.34 ± 5.27	39.28 ± 3.39
gestational age(months)	35 ± 1.21*	38 ± 1.25
Sex		
Male%	7869.03	1669.57
Female%	3530.97	730.43
Age of the mother at birthyears	27.45 ± 1.23	26.34 ± 3.24
Age of the father at birth years	28.53 ± 1.87	28.23 ± 2.87
Birth weight (kg)	2.7 ± 0.4*	3.3 ± 0.2

Table 1: The demographic of spastic cerebral palsic children and healthy control *P<0.05

Parameters	Conventional rehabilitation group	ILF-TMS Treatment group
Number of Participants	53	60
Age (months)	41.849.58	40.846.93
gestational age(months)	361.11	352.12
Sex		
Male%	3566.04	4371.67
Female%	1833.96	1728.33
Age of the mother at birthyears	27.543.24	27.365.25
Age of the father at birthyears	28.182.68	28.933.19
Birth weight (kg)	2.60.5	2.80.3
Delivery type%		
Natural childbirth	1528.3	1220
Cesarean section	3871.7	4880
History of birth asphyxia		
No%	3566.04	3863.33
Yes%	1833.96	2236.67
History of pathologic jaundice after birth		
No%	4381.13	5083.33
Yes%	1018.87	1016.67

Table 2: The demographic of conventional rehabilitation group and ILF-TMS treatment group

The relative power of neurotransmitters in spastic cerebral palsic children and healthy control

Neurotransmitters in the brain were recorded with EFG at time points before, 1 month and 3 months after treatment. The results showed that the relative power of GABA in spastic cerebral palsic children was lower than healthy controls and was increased significantly 3 months after ILF-TMS treatment when compared with pre-treatment (P<0.05, respectively, Figure 1A). The relative power of Glutamate in spastic cerebral palsic children was higher than healthy controls and was reduced significantly 1 month and 3 months after ILF-TMS treatment when compared with pre-treatment, respectively. (P<0.05, respectively, Figure 1B). While there was no significant difference was found about the relative power of 5-HT, Ach, NE and DA between spastic cerebral palsic children and healthy controls.

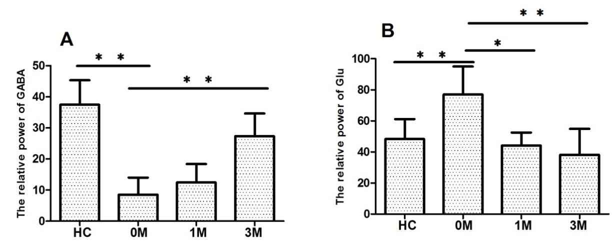

Figure 1: The relative power of GABA and Glu; (A) The changes of relative power of GABA in spastic cerebral palsy after ILF-TMS treatment for 3 months. (B) The changes of relative power of glutamate in spastic cerebral palsy after ILF-TMS treatment for 3 months (*P<0.05,**P<0.01).

The results of gross motor function were assessed by the GMFM

Gross motor function was assessed using the GMFM. No significant difference in the demographic data and pre-training baseline measures between two groups was found. We analyzed GMFM scores at each of the five dimensions for each child at timepoints as before, 1 month and 3 months after treatment, respectively.

The GMFM scores at each of the five dimensions (dimension A: Lying/rolling, dimension B: Sitting, dimension C: Crawling/kneeling, dimension D: Standing, dimension E: Walking/running/jumping) and total scores had an increasing tendency during the treatment in these two groups, however the improvement of gross mobility function in ILF-TMS treatment group was better than that in conventional rehabilitation group. The results indicated there was a significant difference in the scores in ILF-TMS treatment group compared to the conventional rehabilitation group for dimension B after treatment for1 month (P<0.05) (Figure 2A). Three months after training period significant improvement in ILF-TMS treatment group for dimension B (P<0.05), dimension C (P<0.05) and dimension D (P<0.05) of the GMFM was found compared to conventional rehabilitation group (Figure 2B and 2C).

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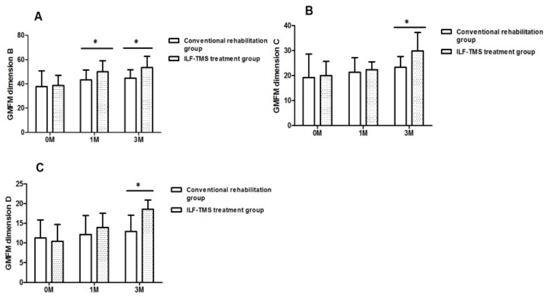

Figure 2: Results of Gross motor function assessed by GMFM in ILF-TMS group and conventional rehabilitation group (A) The changes of dimension B in GMFM in ILF-TMS group and conventional rehabilitation group (B) The changes of dimension C in GMFM in ILF-TMS group and conventional rehabilitation group (C) The changes of dimension D in GMFM in ILF-TMS group and conventional rehabilitation group (*P<0.05).

The results of fine motor function were assessed using the FMFM

Fine motor function was assessed using the FMFM. No significant difference in the demographic data or pre-training baseline measures between two groups was found. We analyzed FMFM scores at each of the five dimensions for each child before and after treatment.

The FMFM scores at each of the five dimensions (dimension A: visual tracking, performance, dimension E: Coordination ability between hands and eyes) and fine motor ability score had an increasing tendency during the treatment in these two groups. Furthermore, the improvement of fine mobility function in LIF-TMS treatment group was better than in conventional rehabilitation group. Moreover, no significant difference was found 1 month after treatment between the two groups. The results indicated that there was an significant differences in the scores in ILF-TMS treatment group when compared to the conventional rehabilitation group for dimension A and dimension B 3 months after treatment (P<0.05, respectively, Figure 3A and 3B).

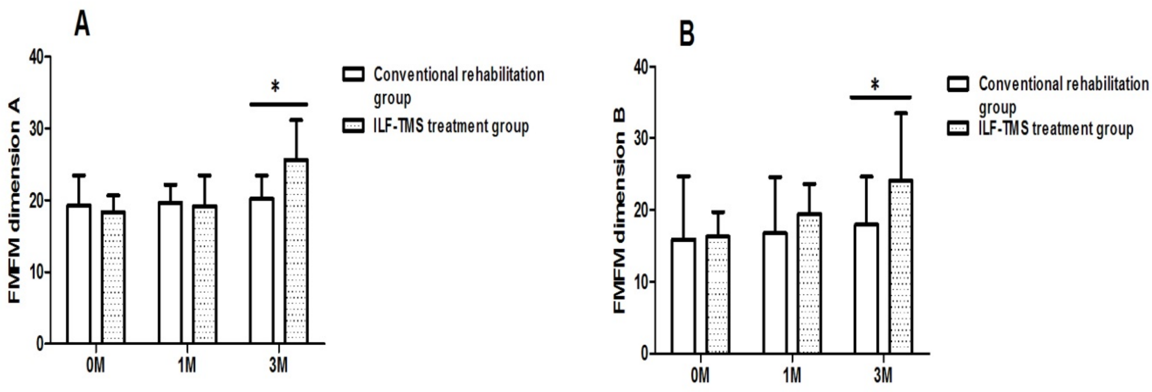

Figure 3: Results of Gross motor function assessed by FMFM in ILF-TMS group and conventional rehabilitation group (A) The changes of dimension A in GMFM in ILF-TMS group and conventional rehabilitation group (B) The changes of dimension B in GMFM in ILF-TMS group and conventional rehabilitation group (*P<0.05)

The results of Intelligence structure were assessed by the GMFM

Intelligence structure was assessed using the GDS. No significant difference in the demographic data or pre-training baseline measures between the two groups was found. We analyzed the GDS scores at each of the five domains for each child before and after treatment.

The GDS scores at each of the five domains (domain A: Gross motor DA/DQ, domain B: Fine motor DA/DQ, domain C: object adaptive ability DA/DQ, domain D: Speaking DA/DQ, domain E: personalsocial behavior DA/DQ) had an increasing trend after treatment in two groups. The results indicated that there was a significant differences in the scores in LIF-TMS treatment group compared to conventional rehabilitation group for gross motor DA and gross motor DQ 3 months after treatment (P<0.05, respectively, Figures 4A and 4B). However, no difference about domain B, domain C and domain D was found between two groups.

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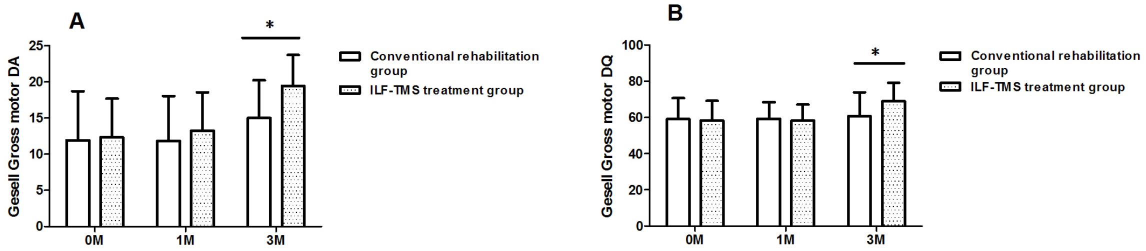

Figure 4: Results of intelligence structure assessed by GDS in ILF-TMS group and conventional rehabilitation group (A) The changes of gross motor DA in GDS in ILF-TMS group and conventional rehabilitation group (B) The changes of gross motor DQ in GDS in ILF-TMS group and conventional rehabilitation group ($^{*}P<0.05$).

Discussion

The main findings in this study are: 1. the relative power of GABA in spastic cerebral palsy is lower than that in healthy controls and is increased significantly after ILF-TMS treatment for 3 months; the relative power of glutamate in spastic cerebral palsy is higher than that in healthy controls and is reduced significantly after ILF-TMS treatment for 3 months. 2. ILF-TMS treatment has improved the performance of CP children on GMFM and FMFM.

Preterm infants markedly increase the risk of CP. Studies examined risk factors in preterm infants [39-41]. Risk factors classically associated with CP in term infants such as preeclampsia, male gender, neonatal sepsis and Apgar scores were less important in preterm infants. Absence of antenatal steroids, growth restriction, and adverse events in the newborn period such as prolonged hypocarbia and postnatal steroids assume greater importance.

CP plays a serious burden to the individual family and society. Children and their families require significant additional support from medical, educational and social systems. The most important treatment at present for CP is timely, long-term, standardized rehabilitation training. Our research has shown that comprehensive rehabilitation can improve the development quotient and five domains including gross motorfine motoradaptationlanguage and individual-social domains. This demonstrates that conventional rehabilitation is still an important method for treatment of cerebral palsy [42].

GABA and glutamate are the two basic neurotransmitters in the brain in the mammalian central nervous system [43-46]. GABA is not only functionally but also metabolically linked with its excitatory counterpart glutamate,as glutamine is the precursor of both. GABA and glutamate, once released from neurons, are taken up into astrocytes, which convert glutamate into glutamine. Impairments of these glial-neuronal interactions result in nervous system diseases[47,48]. They were closely related with advanced functions such as memory, learning and cognition.

The results have shown that the relative power of GABA in brain in spastic cerebral palsy was lower than that in healthy controls and the relative power of Glutamate was higher than that of healthy controls. The changes of GABA and glutamate recorded with EFG in CP children are consistent with previous studies [49-53]. In this study, we use the conventional rehabilitation treatment combined with ILF-TMS treatment on spastic cerebral palsy. Neurotransmitter in the brain was recorded with EFG. We use the ILF-TMS treatment to improve the balance between GABA and Glu in the spastic cerebral palsic children. The relative power of GABA in spastic cerebral palsy was increased and Glu was reduced significantly after ILF-TMS treatment for 3 months. We think that ILF-TMS can regulate the function of neurotransmitter by a specific magnetic field generated in the brain. ILF-TMS has been reported in the central nervous system diseases widely [54,55].

Several reports have demonstrated that low frequency rTMS facilitates the recovery of motor function in children with a brain injury, suggesting that rTMS is a useful modality to improve the motor in disable patient due to cerebral impairment [56,57]. However, no paper about the effect of ILF-TMS treatment on the changes of motor function in spastic cerebral palsy has been reported. In this study, we use A battery of instruments such as of GMFM, FMFM and GDS to comprehensively evaluate the performance of CP children treated with ILF-TMS treatment. Analysis of the scores in the three tasks indicates that the children treated with ILF-TMS have performed better than those in the conventional rehabilitation group. To the best of our knowledge, this is the first report that ILF-TMS treatment can restore the balance of neurotransmitters such as GBAB and glutamate and improve the motor function and intelligence in children with CP. We deduce that ILF-TMS treatment maybe improve the intelligence structure and motor function in CP children through regulating neurotransmitters in brain.

There are some shortcomings of our present study such as small samples and short-term ILF-TMS intervention. A further larger sample and long-term study for ILF-TMS treatment for CP children is warranted. Above all, the present study has shown that ILF-TMS is effective in improve the motor function and maybe is a worthwhile choice in the treatment for CP children.

Acknowledgements

We thank all the children who were participated in our study and their parents and/or caregiver's support and Kangli-tech company limited (Shenzhen, China) who provided Ultra-low frequency transcranial magnetic stimulator.

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