

Transcranial magnetic stimulation A case report and review of the literature

P. ANNINOS*, A. KOTINI*, D. TAMIOLAKIS** and N. TSAGAS***

*Lab of Medical Physics, Medical School, Democritus University of Thrace, University Campus, Alexandroupolis, Greece;

General Hospital of Chania, Crete, Greece; *Lab of Nuclear Technology, Dept of Electrical Engineering and Computer Technology, Democritus Univ. of Thrace, GR-67100, Greece

Abstract

Objective : Transcranial magnetic stimulation (TMS) is a non-invasive tool for the electrical stimulation of neural tissue. TMS can be applied as single pulses of stimulation, pairs of stimuli separated by variable intervals to the same or different brain areas, or as trains of repetitive stimuli at various frequencies.

Case report : A 2-years-old male infant was referred to our department with a history of Epstein-Barr virus (EBV) encephalitis, treated with foscarnet and steroids, for he developed mutism and ataxia and loss of the ability to eat, walk and talk. Brain imaging revealed loss of white matter around ventricles and progressive global brain atrophy, findings consistent with encephalopathy. Serology for antibodies against EBV infection was positive and the diagnosis of acute and prolonged EBV infection was made. There was an improvement of the clinical findings after the application of TMS with proper field characteristics (intensity : 1-7.5 pT, frequency : 8-13 Hz).

Conclusions : Our case illustrates the possibility of therapeutic applications of TMS (in the order of pT) with proper field characteristics to normalize pathologically decreased levels of brain cortex activity. TMS might provide novel insights into the pathophysiology of the neural circuitry, be developed into clinically useful diagnostic and prognostic tests, and have therapeutic uses in various diseases.

Key words : MEG ; TMS ; Epstein-Barr virus encephalitis.

Transcranial magnetic stimulation (TMS) as currently used, was introduced by Barker *et al.* (1) TMS provided for the first time a non-invasive, safe and painless method of activating the human motor cortex and assessing the integrity of the central motor pathways. Since its introduction, the use of TMS in clinical neurophysiology, neurology, neuroscience and psychiatry has spread widely, mostly in research applications, but increasingly with clinical aims in mind (2, 3).

Anninos *et al.* (4-7) applied external TMS (in the order of pico Tesla) with proper field characteristics (intensity : 1-7.5 pT, frequency : 8-13 Hz) in the frontal, occipital and temporal lobes of the patients for the treatment of epilepsy, Parkinson disease, multiple sclerosis etc using an electronic device. This electronic device consists of a low voltage generator, which can produce low frequencies from 2-13 Hz to a group of coils of 1 cm diameter (Anninos & Tsagas inventors (7)). The 32 coils are enclosed between two parallel plane surfaces in such a way that the axis of the coils is situated perpendicular to these surfaces. They are situated on the 32-point matrix, which is defined previously. The applied TMS carried similar field characteristics (intensity : 1-7.5 pT and frequency 8-13 Hz) with the ones emitted from the patient's brain measured by magnetoencephalography (MEG) prior of the application of TMS.

TMS can be applied as single pulses of stimulation, pairs of stimuli separated by variable intervals to the same or different brain areas, or as trains of repetitive stimuli at various frequencies. Single stimuli can depolarize neurons and evoke measurable effects. Repetitive TMS can modify excitability of the cerebral cortex at the stimulated site and also at remote areas along functional anatomical connections (8). With any new medical tool we ought to ask ourselves what it can offer that established methods do not for diagnostic, prognostic and therapeutic parts of clinical neurology. A new neurological tool might have several benefits : establishment of a differential diagnosis earlier or with greater certainty for a given clinical presentation than existing methods; better prediction of the likely course of the disease; further support for sustained and intensive interventions; help in identification of the most suitable treatment strategy; or improvement of clinical outcome as a therapy itself.

The main clinical application of TMS concerns testing of the functional integrity of the corticospinal tract in patients with disorders affecting the

CNS. Use of standard TMS in these neurological disorders provides information on detection of sub-clinical upper motorneuron involvement, localization of anatomical site of lesions, longitudinal monitoring of motor abnormalities during course of diseases, and valuable aid to differential diagnosis. Repetitive stimulation of the brain opens a new field of investigations of cognitive function and mood and of therapeutic possibilities. There are interesting results in the short-term treatment of refractory depression by daily sessions of repetitive TMS. By changing the frequency of stimulation, it may be possible to modulate cortical excitability for therapeutic benefit. The ability of TMS to measure and modify cortical activity offers possibilities to apply this methodology to clinical neurology, neurorehabilitation and psychiatry (9).

TMS in clinical neurology

MULTIPLE SCLEROSIS

Various abnormalities can be observed in multiple sclerosis (MS) that relate to demyelination and to axonal loss. Demyelination of central motor pathways induces slowed conduction or conduction block. The latency of motor evoked potentials (MEPs) can be prolonged and the response may be dispersed, of smaller size, or absent. A reduced MEP size may indicate a central conduction deficit, but this relation is obscured by the desynchronization of the descending action potentials in response to TMS that eliminates these effects allows quantification of conducting central motor neurons. Thereby, it increases the sensitivity to detect a central motor conduction deficit. The motor threshold can be moderately increased in MS. The silent period is usually prolonged. Data that concern cortical excitability changes seem of little clinical value (10-14, 9).

CERVICAL SPONDYLOTIC MYELOPATHY

Cervical spondylotic myelopathy (CSM) is characterized by a marked and early CMCT prolongation. Sometimes clinically, and with routine electroneuromyography (ENMG) examination, distinction between CSM and amyotrophic lateral sclerosis (ALS) may be difficult. These disorders, that impair both upper and lower motorneurons, may share similar clinical features, including muscle wasting and fasciculation. TMS enables to distinguish these disorders (15, 9).

DEPRESSION

Treatment of depression is the most thoroughly studied of the potential clinical applications of repetitive TMS. Lasting beneficial effects have been seen in about 40% of patients with medica-

tion-resistant depression in recent studies (16). Both high frequency rTMS of the left dorsolateral prefrontal cortex and low frequency stimulation of the right side can improve depression.

PARKINSON

Pascual-Leone *et al.* (17) first reported that in 5 patients with Parkinson's disease submotor-threshold rTMS at high frequency (5Hz) to the motor cortex improved contralateral hand function. There are two rationales for trials of this method in Parkinson's disease: first, increasing cortical excitability to thalamocortical drive, which is believed to be lacking in the disease; and second, modifying catecholamine metabolism subcortically through cortical stimulation (5, 18).

DYSTONIA

After physiological studies of task-specific dystonia suggested hyperexcitability of the motor cortex or a failure of intracortical inhibition, rTMS of the motor cortex at 1 Hz has been used to treat patients with writer's cramp 19. The improvement of deficient intracortical inhibition and handwriting lasted at the most 3h after application of a 30 min train of TMS but resulted in clinical benefits in only 2 of 16 patients studied. In tic disorder, a similarly abnormal increase of cortical excitability is reported and 1Hz rTMS of the motor cortex can reduce the frequency of tics 20.

FACIAL PALSIES

The clinical and electrophysiological spectrum of facial palsies is broad and differential diagnosis may be difficult. The lesion of the facial nerve frequently lays within the skull, where the nerve is not accessible to conventional electrical stimulation. TMS changed this situation, because the proximal intracranial part of the facial nerve and the contralateral hemisphere facial associated cortex became accessible to stimulation (21-23, 9).

EPILEPSY

TMS has been used to study generalized and focal epilepsies. Different results probably relate to the multiform types of epilepsies, the presence of drugs and the different techniques used. The most common abnormality in the motor cortex of patients investigated with paired-pulse TMS, is an increased excitability with a reduction of intracortical inhibitory mechanisms. TMS proved useful to test the mode of action and the responsivity to antiepileptic drugs (4, 6, 9, 24-26).

STROKE

Outcome after stroke may be favorably influenced by rTMS suppressing maladaptive cortical plasticity and improving adaptive cortical activity to promote neuro-rehabilitation. Functional imaging studies after stroke show increased activity in undamaged brain areas (27) but the role of these areas is controversial.

SCHIZOPHRENIA

TMS research has provided inconclusive results concerning corticospinal conductivity in schizophrenia. In the first study of motor function in schizophrenia using TMS, Puri *et al.* (29) detected a significantly shorter latency of MEPs in nine unmedicated patients with schizophrenia compared to nine healthy subjects. However, further studies measuring MEP latency did not find a difference between medicated schizophrenia patients and normal controls (28, 29).

Case Report

Approximately 1-5% of patients with acute primary infections due to Epstein-Barr virus are believed to develop neurological complications such as meningitis, encephalitis, acute demyelinating encephalomyelitis, cranial nerve palsy, cerebellitis, myelitis, or visual seizures with metamorphopsia (30). Therefore, a search for acute primary EBV infections is well established in patients with central nervous system (CNS) diseases (31). In contrast, neurological disease complicating the course of chronic active EBV infections or occurring in immunocompetent pediatric patients with reactivated EBV infections has been described only rarely.

A 2-year-old male infant was referred to our department with a 20-day history of Epstein-Barr virus (EBV) encephalitis, treated with foscarnet (foscavir 450 mg \times 3 per day) and steroids (medrol 8 mg \times 4 per day). Treatment was employed for approximately one month and was stopped due to intense tremor side-effect. The patient developed mutism and ataxia and loss of the ability to eat, walk and talk. Brain imaging revealed loss of the white matter around ventricles and slightly progressive global brain atrophy, findings similar to the ones at onset of disease and consistent with encephalopathy. Serology for antibodies against EBV was positive for acute infection (VCA-IgM positive, VCA-IgG = 1/320, anti-EBNA less than 1/20, and EA-IgG less than 1/40). No other causative agents were detected by the laboratory work-up including the ones for metabolic diseases. Nested polymerase chain reaction (PCR) testing, was negative for EBV DNA in the cerebrospinal fluid. Subsequently, he was evaluated

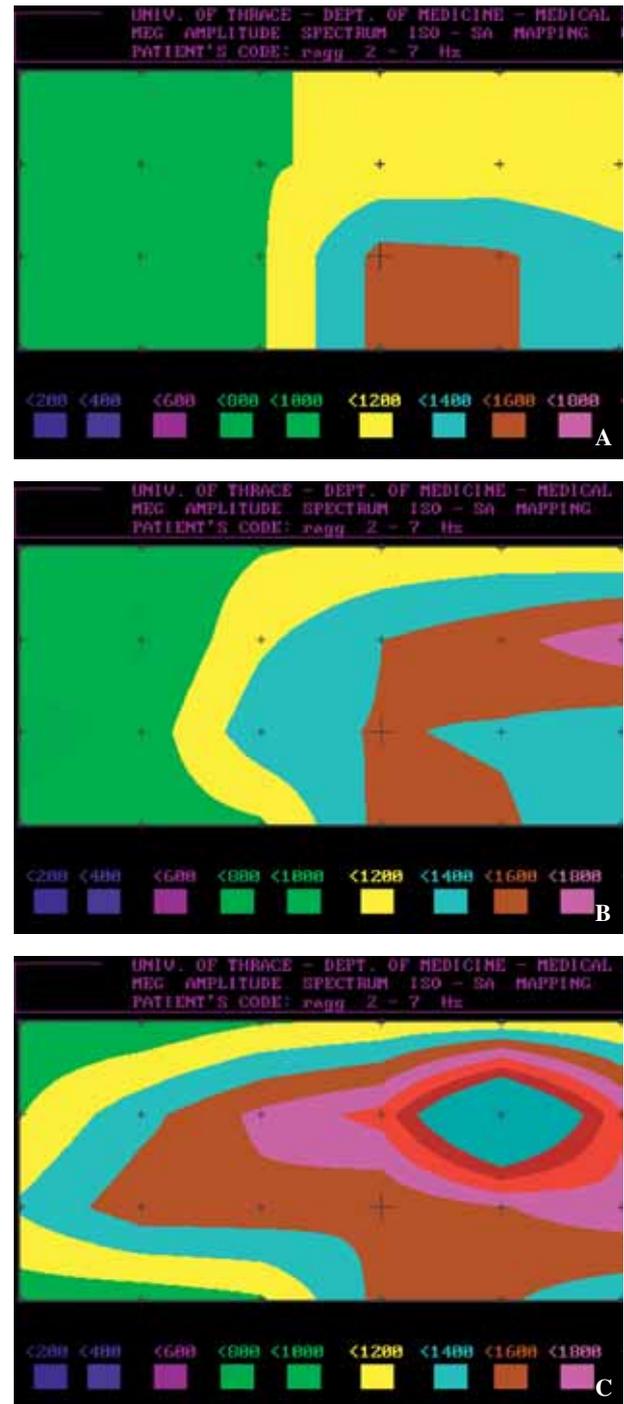


FIG. 1. — A) The MEG map of the right temporal area of the patient with biomagnetic values $< 1600 \text{ Ft}/\sqrt{\text{Hz}}$. B) The MEG map after 2-years treatment with TMS. The biomagnetic values were $< 1800 \text{ Ft}/\sqrt{\text{Hz}}$. C) The MEG map after 3-years treatment with TMS with biomagnetic values $> 2200 \text{ Ft}/\sqrt{\text{Hz}}$.

with MEG. Informed consent was obtained from his parents prior to the procedure. The spatial distribution of the amplitude of MEG power spectrum was examined using computer-generated graphics and expressed in terms of the total average of iso-contour spectral amplitude distribution (ISO-SA) on the surface of the scanned areas over the scalp in the 2-7 Hz band frequencies. Different colors

represent different spectral amplitudes. TMS sessions (in the order of pico Tesla) were repeated 2 times a week for 3 years with the electronic device that Anninos & Tsagas invented (7). There was an improvement of the clinical findings after the application of TMS. Fig. 1A demonstrates the MEG map of the right temporal area of the patient with biomagnetic values $< 1600 \text{ Ft}/\sqrt{\text{Hz}}$. Fig. 1B shows the MEG map after 2 years completion of TMS sessions. The biomagnetic values were $< 1800 \text{ Ft}/\sqrt{\text{Hz}}$. Fig. 1C shows the MEG map after 3-years treatment with TMS with biomagnetic values $> 2200 \text{ Ft}/\sqrt{\text{Hz}}$.

Our case provides useful insights into therapeutic employment of TMS in neurology. The clinical improvement suggests that TMS is efficacious in EBV encephalitis related sequelae.

REFERENCES

- BARKER A. T., JALINOUS R., FREESTON I. L. Non-invasive magnetic stimulation of human motor cortex. *Lancet*, 1985, **1** : 1106-1107.
- GEORGE M. S., BELLMAKER R. H. *Transcranial magnetic stimulation in neuropsychiatry*. Washington DC : American Psychiatric Press, 2000.
- WALSH V., PASCUAL-LEONE A. *Neurochronometrics of mind : TMS in cognitive science*. Cambridge, MA : MIT Press, 2003.
- ANNINOS P. A., TSAGAS N., JACOBSON J. I., KOTINI A. The biological effects of magnetic stimulation in epileptic patients. *Panminerva Med.*, 1999, **41** : 207-215.
- ANNINOS P., ADAMOPOULOS A., KOTINI A., TSAGAS N. Nonlinear Analysis of Brain Activity in Magnetic Influenced Parkinson Patients. *Brain Topogr.*, 2000, **13** : 135-144.
- ANNINOS P. A., TSAGAS N., SANDYK R., DERPAPAS K. Magnetic stimulation in the treatment of partial seizures. *Int. J. Neurosci.*, 1991, **60** : 141-171.
- ANNINOS P. A., TSAGAS N. Electronic apparatus for treating epileptic individuals, US patent number 5,453,072, Sept 26, 1995.
- KOBAYASHI M., PASCUAL-LEONE A. Transcranial magnetic stimulation in neurology. A review. *The Lancet Neurol.*, 2003, **2** : 145-156.
- ALIŠAUSKIENĖ M., TRUFFERT A., VAIČIENĖ N., MAGISTRIS M. R. Transcranial magnetic stimulation in clinical practice. *Medicina (Kaunas)*, 2005, **41** (10) : 813-824.
- HESS C. W., MILLS K. R., MURRAY N. M. F., SCHRIEFER T. N. Magnetic brain stimulation : central motor conduction studies in multiple sclerosis. *Ann. Neurol.*, 1987, **22** : 744-52.
- BRITTON T. C., MEYER B. U., BENECKE R. Variability of cortical evoked motor responses in multiple sclerosis. *Electroencephalogr. Clin. Neurophysiol.*, 1991, **81** : 186-94.
- TATAROGLU C., GENÇ A., IDIMAN E., ÇAKMUR R., IDIMAN F. Cortical silent period and evoked potentials in patients with multiple sclerosis. *Clin. Neurol. Neurosurg.*, 2003, **105** : 105-10.
- SCHMIERER K., IRLBACHER K., GROSSE P., RORICHT S., MEYER B. U. Correlates of disability in multiple sclerosis detected by transcranial magnetic stimulation. *Neurology*, 2002, **59** : 1218-24.
- SCHMIERER K., NIEHAUS L., RORICHT S., MEYER B. U. Conduction deficits of callosal fibers in early multiple sclerosis. *J. Neurol. Neurosurg. Psychiatry*, 2000, **68** : 633-8.
- TRUFFERT A., RÖSLER K. M., MAGISTRIS M. R. Amyotrophic lateral sclerosis versus cervical spondylotic myelopathy : a study using transcranial magnetic stimulation with recordings from the trapezius and limb muscles. *Clin. Neurophysiology*, 2000, **111** : 1031-8.
- WASSERMANN E. M., LISANBY S. H. Therapeutic application of repetitive transcranial magnetic stimulation : a review. *Clin. Neurophysiol.*, 2001, **112** : 1367-1377.
- PASCUAL-LEONE A., VALLS-SOLE J., BRAZIL-NETO J. P., CAMMAROTA A., GRAFMAN J., HALLETT M. Akinesia in Parkinson's disease, II : effects of subthreshold repetitive transcranial motor cortex stimulation. *Neurology*, 1994, **44** : 892-898.
- BEN-SHACHAR D., GAZAWI H., RIBOYAD-LEVIN J., KLEIN E. Chronic repetitive transcranial magnetic stimulation alters beta-adrenergic and 5-HT₂ receptor characteristics in rat brain. *Brain Res.*, 1999, **816** : 78-83.
- SIEBNER H. R., TORMOS J. M., CEBALLOS-BAUMANN A. O. *et al.* Low-frequency repetitive transcranial magnetic stimulation of the motor cortex in writer's cramp. *Neurology*, 1999, **52** : 529-537.
- KARP B. I., WASSERMANN E. M., PORTERS S., HALLETT M. Transcranial magnetic stimulation acutely decreases motor tics. *Neurology*, 1997, **48** : A397.
- RÖSLER K. M., HESS C. W., SCHMID U. D. Investigation of facial motor pathways by electrical and magnetic stimulation : sites and mechanisms of excitation. *J. Neurol. Neurosurg. Psychiatry*, 1989, **52** : 1149-56.
- RÖSLER K. M., MAGISTRIS M. R., GLOCKER F. X., KOHLER A., DEUSCHL G., HESS C. W. Electrophysiological characteristics of lesions in facial palsies of different etiologies. A study using electrical and magnetic stimulation techniques. *Electroencephalogr. Clin. Neurophysiol.*, 1997, **97** : 355-68.
- GLOCKER F. X., MAGISTRIS M. R., RÖSLER K. M., HESS Ch. W. Electrical stylomastoidal and magnetic transcranial stimulation of the facial nerve in Bell's palsy. *Electroencephalogr. Clin. Neurophysiol.*, 1994, **93** : 113-20.
- LIEPERT J., WESSEL K., SCHWENKREIS P., TRILLENBERG P., OTTO V., VORGERD M. *et al.* Reduced intracortical facilitation in patients with cerebellar degeneration. *Acta Neurol. Scand.*, 1998, **98** : 318-23.
- MACDONELL R. A., CURATOLO J. M., BERKOVIC S. F. Transcranial magnetic stimulation and epilepsy. *J. Clin. Neurophysiol.*, 2002, **19** : 294-306.
- ZIEMANN U., LONNECKER S., STEINHOFF B. J., PAULUS W. Effects of antiepileptic drugs on motor cortex excitability in humans : a transcranial magnetic stimulation study. *Ann. Neurol.*, 1996, **40** : 367-78.

27. MARSHALL R. S., PERERA G. M., LAZAR R. M., KRAKAUER J. W., CONSTANTINE R. C., DELAPAZ R. L. Evolution of cortical activation during recovery from corticospinal tract infarction. *Stroke*, 2000, **31** : 656-661.
28. BOROOJERDI B., TOPPER R., FOLTYS H., MEINCKE U. Transcallosal inhibition and motor conduction studies in patients with schizophrenia using transcranial magnetic stimulation. *Br. J. Psychiatry*, 1999, **175** : 375-379.
29. PURI B. K., DAVEY N. J., ELLAWAY P. H., LEWIS S. W. An investigation of motor function in schizophrenia using transcranial magnetic stimulation of the motor cortex. *Br. J. Psychiatry*, 1996, **169**, 6 : 690-695.
30. JENSON H. B. Acute complications of Epstein-Barr virus infectious mononucleosis. *Curr. Opin. Pediatr.*, 2000, **12** : 263-268.
31. COHEN J. I. Epstein-Barr virus infection. *N. Engl. J. Med.*, 2000, **343** : 481-492.

Em. Prof. P. ANNINOS,
Laboratory of Medical Physics, Medical School,
Democritus University of Thrace,
University Campus,
68100, Alexandroupolis (Greece).
E-mail : anninos@axd.forthnet.gr