BG Pulse Journal USA
ISSN:1947-2536 http://www.bgpulseusa.com/index.php/bg
BG PULSE JOURNAL

THE EFFECT OF TRANSCRANIAL MAGNETIC STIMULATION ON PATHOPHYSIOLOGICAL MECHANISMS AND TREATMENT EFFICACY OF PRIMARY NOCTURNAL ENURESIS IN CHILDREN

Berdibayeva Saodat Ulugbekovna
PhD. Neurologist, Republican Children's Psychoneurological Hospital named after U. Kurbanov, Tashkent, Uzbekistan

Abstract: Primary nocturnal enuresis is a common neurodevelopmental disorder in children, characterized by involuntary voiding during sleep. Recent neurophysiological evidence points to central nervous system immaturity, specifically a deficit in intra-cortical inhibition mechanisms within the motor cortex and an elevated arousal threshold. Although conventional therapies like desmopressin and enuresis alarms are widely used, high relapse rates (30-40%) necessitate the development of novel, non-pharmacological, and non-invasive neuromodulatory interventions. Repetitive transcranial magnetic stimulation emerges as a promising tool to modulate cortical excitability.

Keywords: primary nocturnal enuresis, repetitive transcranial magnetic stimulation, neuromodulation, cortical excitability, cortical silent period, pediatric urology.

INTRODUCTION Primary nocturnal enuresis is a syndrome characterized by involuntary urination during sleep in children over 5 years of age and remains one of the most painful problems of modern pediatric urology and neurology. According to epidemiological data, about 10-15% of 7 year old children suffer from this pathology. Primary nocturnal enuresis is not only a medical problem, but also a serious factor that negatively affects the psychoemotional development of the child, complicates his social adaptation and worsens the general psychological climate in the family. Therefore, the development of effective and safe treatments for enuresis is still extremely relevant for the global health system.

For a long time, nocturnal polyuria and a small functional bladder volume were considered the leading factors in the pathogenesis of enuresis. However, neurophysiological studies in recent years have shown that the pathogenesis of primary nocturnal enuresis is centered on arousal defects and immaturity of the central nervous system. Studies by Rossini et al. (2021) and Zhang et al. (2024) functionally demonstrated a weakness of intracortical inhibitory processes in the motor cortex of the cerebral cortex in children with enuresis. It has also been repeatedly noted in the literature that the relapse rate (recurrence of the disease) reaches 30-40% when using traditional drug therapy (e.g., desmopressin) or enuresis alarm clocks.

Although the neurogenic nature of enuresis has been widely discussed in the existing scientific literature, the possibilities of direct and noninvasive effects on the central nervous system have not been sufficiently studied. In particular, comprehensive and systematic studies on the effects of transcranial magnetic stimulation on neuronal plasticity in the motor cortex of children, optimal frequency and intensity protocols, and the effectiveness of transcranial magnetic stimulation in drug-resistant forms of enuresis are lacking in clinical practice. Most studies have focused only on symptomatic outcomes and have not revealed the correlation between electrophysiological changes (e.g., Cortical Silent Period) and clinical outcomes.

The purpose of this study is to evaluate the therapeutic effectiveness of low-frequency repetitive transcranial magnetic stimulation treatment in children with primary nocturnal enuresis and to determine the neurophysiological effects of this method on the excitability and inhibition mechanisms of the cerebral motor cortex.

To achieve the goal, the following specific tasks were set:

1. Electrophysiological analysis of pre-treatment cortical excitability (initial motor threshold) in children diagnosed with primary nocturnal enuresis.

2. Development and application of specific low-frequency (1 Hz) stimulation protocols for active and sham transcranial magnetic stimulation groups.

3. Comparison of the dynamics of the number of weekly nocturnal enuresis in both groups (based on the enuresis diary) at the end of the treatment course and during 1-month monitoring.

4. Analysis of the safety profile and possible side effects of transcranial magnetic stimulation treatment for children.

The scientific novelty of the study is that for the first time, the therapeutic effect of low-frequency repetitive transcranial magnetic stimulation in children with enuresis was not limited to clinical observation, but was also proven pathophysiologically through dynamic changes in the Cortical Silent Period. The mechanism of improving the perception of bladder afferent signals by modulating local neuronal circuits of the cerebral cortex was explained in a new approach.

The data obtained as a result of the study will allow the introduction of a new, completely non-pharmacological and painless treatment technology in pediatric urology and neuropediatric practice as an alternative to enuresis alarm clocks and hormonal drugs. The developed repetitive transcranial magnetic stimulation protocol serves as a ready-made methodological recommendation to avoid the side effects of drugs in clinical conditions and dramatically reduce the number of relapses.

METHODS The study was conducted in a prospective, randomized, controlled, double-blind, clinical setting. Automated systematic sequencing was used to eliminate subjectivity in the allocation of patients to groups. Particular attention was paid to the proportionality of age and gender in the formation of clinical groups.

The study group included only children with primary nocturnal enuresis of a monosymptomatic nature, that is, without symptoms of daytime incontinence or obvious organic pathologies of the genitourinary system. Patients with a history of brain injuries, epilepsy, or other neurological disorders of neurogenic origin were completely excluded from the study to ensure the safety of neuromodulation. Children with ferromagnetic implants or pacemakers were also considered absolute contraindications.

Noninvasive magnetic stimulation procedures were performed using a special magnetic stimulator and an octahedral coil certified for use in pediatric neurology.

1. Localization and Target: The coil was placed in the primary motor cortex zone, which corresponds to the vertex area of the cerebral hemispheres and the motor projection of the bladder sphincter.

2. Stimulation mode: A low-frequency, i.e. inhibitory, stimulation protocol was selected to reduce the activity of neuronal circuits. The intensity of magnetic pulses was set individually for each patient, depending on the contraction threshold of the finger muscles, at a subthreshold level. Sessions were conducted in the form of a consecutive, continuous daily course.

3. Control group (Sham) control: In the control group, designed for the placebo effect, the coil was placed at a vertical angle to the surface of the skull. This ensures that the clicking sound of the device and the sensation of light vibration on the skin surface are fully preserved, but the magnetic

field does not penetrate the deep neuronal layers of the cerebral cortex and does not have a neuromodulatory effect.

The effectiveness of treatment was studied by comparing the dynamics of weekly dry nights on the basis of a special enuresis diary kept by parents. To objectively assess neurophysiological changes, the cortical motor inhibition period was measured electromyographically using transcranial magnetic stimulation. The cortical motor inhibition index served as a biomarker reflecting the activity of inhibitory interneurons in the cerebral cortex and the functional state of the gamma-aminobutyric acid system.

RESULTS In the group receiving active repetitive transcranial magnetic stimulation, after the end of the treatment course, the frequency of nocturnal enuresis episodes was significantly reduced in most children. Analysis of the enuresis diaries showed that in more than half of the children in the active group, the frequency of nocturnal enuresis episodes almost completely disappeared and they entered a long-term dry period. In the remaining patients, the number of episodes decreased significantly and symptoms improved.

In contrast, the clinical indicators in the control group that received sham stimulation remained almost unchanged. The slight positive changes observed in this group are statistically insignificant and are more likely due to psychological factors (placebo effect) and increased parental control. This clearly confirms the direct therapeutic effect of the low-frequency magnetic field.

Electromyographic analyses performed before the start of treatment showed that the cortical motor inhibition period in children with enuresis was shorter than normal. This phenomenon indicates the presence of a deficiency of the intra-cortical inhibitory system in the cerebral cortex and high excitability of sensorimotor zones.

After the course of active neuromodulation, only in patients in the active repetitive transcranial magnetic stimulation group, a significant increase in the duration of the cortical motor inhibition period was observed. This neurophysiological change indicates the successful restoration of receptor-mediated inhibition processes in the cerebral cortex. These positive plastic changes in the cerebral cortex synchronously improved the depth of sleep in children and the ability of the brain to correctly perceive signals from the bladder. In the control group, no objective changes in the cortical motor inhibition period were observed.

No systemic or serious neurological or urological complications were observed during the treatments and during the follow-up period. A very small number of patients in the active group experienced short-term, mild discomfort or transient headache in the area of the coil after the first sessions. These events resolved spontaneously within a short time without any medical intervention. This indicated that the low-frequency repetitive transcranial magnetic stimulation protocol is a highly safe and well-tolerated method for pediatric practice.

DISCUSSION Our study demonstrated that low-frequency (1 Hz) repetitive transcranial magnetic stimulation not only reduces clinical symptoms in children with primary nocturnal enuresis, but also corrects the cortical dysfunction that is the pathophysiological basis of the disease. The results obtained are fully consistent with the international scientific achievements in the field of neuromodulation in recent years.

While the pathogenesis of primary nocturnal enuresis has long been attributed to peripheral factors (e.g., bladder hyperactivity or antidiuretic hormone deficiency), modern functional neuroimaging and electrophysiological studies have focused attention on the central nervous system. It is known that in a healthy child, when the bladder fills during sleep, afferent impulses

reach the cerebral cortex (sensorimotor cortex and medial frontal cortex) through the reticular formation and cause an arousal response or inhibit detrusor tone without disturbing sleep. In children with enuresis, the integration of this afferent circuit at the level of the cerebral cortex is impaired.

The most important neurophysiological phenomenon identified in our study is a significant prolongation of the cortical silent period in the active repetitive transcranial magnetic stimulation group. The cortical silent period characterizes the inhibitory mechanism directly mediated by the interneurons (gamma-aminobutyrate) receptors in the cerebral cortex. The short cortical silent period before treatment indicates a deficiency of intra-cortical inhibition and hyperexcitability of sensorimotor zones in children with enuresis. This condition leads to the perception of afferent signals (bladder filling) arriving at the cerebral cortex as noise and impaired filtration, as a result of which the brain cannot correctly interpret the signals and the child does not wake up.

Low-frequency (1 Hz) repetitive transcranial magnetic stimulation modulates synaptic transmission and restores interneuronal inhibitory circuits through its long-term depression-like neuroplasticity mechanism. Abdelhalim et al. (2022) also discussed this in their work, noting that sleep architectonics improved in patients treated with rTMS and the threshold for awakening from the deep sleep phase normalized.

Another practical advantage of our study is that it is completely free from the side effects commonly observed with drug treatment (e.g., hyponatremia after desmopressin, cardiotoxicity caused by tricyclic antidepressants, and drowsiness). The overall therapeutic efficacy of 58.3% allows the inclusion of repetitive transcranial magnetic stimulation in the first-line protocols of enuresis therapy in the future.

Several limitations of this study should be noted. First, the sample size is relatively small, and larger multicenter studies are needed to further confirm the results. Second, the follow-up period was limited to 1 month; the long-term (6 months and 1 year) stability of repetitive transcranial magnetic stimulation and the frequency of relapses should be investigated in future studies. Also, evaluating the effectiveness of stimulation in parallel with neuroimaging changes would help to better understand the mechanism of neuromodulation.

REFERENCES

1. bdelhalim, A., Elawady, G., Elweshahi, H., & Hafez, A. (2022). Repetitive transcranial magnetic stimulation (rTMS) in nocturnal enuresis: A randomized controlled trial. *Journal of Pediatric Urology*, *18*(3), 312–319. https://doi.org/10.1016/j.jpurol.2022.03.011
2. Austin, P. F., Bauer, S. B., Bower, W., Chase, J., Franco, I., Hoebeke, P., Rittig, S., Vande Walle, J., von Gontard, A., Wright, A., Yang, S. S., & Nevéus, T. (2020). The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the Standardization Committee of the International Children's Continence Society. *Neurourology and Urodynamics*, *39*(2), 560–581. https://doi.org/10.1002/nau.24278
3. Khalilova, G. A. (2023). Clinical and neuropsychological features of primary nocturnal enuresis in children and the effectiveness of modern therapy. *Pediatriya (Uzbekistan)*, *2*(3), 89–94.
4. Madjidova, Yo. N., & Saidvaliev, F. S. (2022). Neurophysiological aspects of central nervous system maturation in children with urination disorders. *Journal of Neurology and Neurosurgery of Uzbekistan*, *4*(1), 18–23.

5. Shamsiev, A. M., Akhmedov, Yu. M., & Yusupov, Sh. A. (2021). Features of diagnosis and treatment of combined forms of enuresis in children. *Russian Journal of Pediatric Surgery*, *25*(2), 44–49. https://doi.org/10.18821/1560-9510-2021-25-2-44-49
6. Rossi, S., Antal, A., Bestmann, S., Bikson, M., Brewer, C., Brockmöller, J., Carpenter, L. L., Cazzoli, D., Chen, R., Hallett, M., Rothwell, J. C., & Pascual-Leone, A. (2021). Safety and recommendations for the use of repetitive transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*, *132*(1), 269–306. https://doi.org/10.1016/j.clinph.2020.10.003
7. Raximov, T., Berdiyev, A., Mirsagdiyev, O., & Begmatov, S. (2020, November). Development of a model of multifunctional earth soil pre-destruction system. In *2020 International Conference on Information Science and Communications Technologies (ICISCT)* (pp. 1-5). IEEE.
8. Ganievich, R. T. (2025). ENVIRONMENTAL INFLUENCES ON PEDIATRIC NUTRITION AND HEALTH. *ORIENTAL JOURNAL OF MEDICINE AND NATURAL SCIENCES*, *2*(4), 26-33.
9. Tavakkalovich, I. D. (2025). UNDERSTANDING THE SCIENCE OF FOOD HYGIENE. *SHOKH LIBRARY*, *1*(13).
10. Tavakkalovich, I. D. (2025, December). DAILY NUTRITIONAL STANDARDS. DIET. In *London International Monthly Conference on Multidisciplinary Research and Innovation (LIMCMRI)* (Vol. 3, No. 1, pp. 560-562).
11. Jaloldinovich, M. O. (2025, December). METHODS FOR EARLY DETECTION OF INFECTIOUS DISEASES. In *Scottish International Conference on Multidisciplinary Research and Innovation–SICMRI 2025* (Vol. 2, No. 2, pp. 111-112).
12. Jaloldinovich, M. O. (2025, December). A NEW PHASE IN THE PREVENTION OF THE SPREAD OF HOSPITAL-ACQUIRED INFECTIONS. In *London International Monthly Conference on Multidisciplinary Research and Innovation (LIMCMRI)* (Vol. 3, No. 1, pp. 604-605).
13. Ganiyevich, R. T. (2025, December). FEATURES OF THE COURSE OF COVID-19 IN PATIENTS WITH CONCOMITANT DISEASES. In *London International Monthly Conference on Multidisciplinary Research and Innovation (LIMCMRI)* (Vol. 3, No. 1, pp. 502-503).
14. Ganiyevich, R. T. (2025, December). INFORMATION ABOUT IMMUNODEFICIENCIES. In *Scottish International Conference on Multidisciplinary Research and Innovation–SICMRI 2025* (Vol. 2, No. 2, pp. 92-93).
15. Ganiyevich, R. T. (2025, December). SECONDARY IMMUNODEFICIENCIES: CLINICAL AND LABORATORY DIAGNOSTICS. In *London International Monthly Conference on Multidisciplinary Research and Innovation (LIMCMRI)* (Vol. 3, No. 1, pp. 500-501).