AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 6. No 03. February ,2026

# TRANSCRANIAL MAGNETIC STIMULATION IN PATIENTS WITH VITAMIN B12 DEFICIENCY ANEMIA AND SEVERE FUNICULAR MYELOSIS

**Gapparova Nilufar**

Resident physician of the neurology department,

Samarkand Regional multi-network medical center

**Kulmirzaeva Khurshida**

Resident physician of the neurology department,

Samarkand Regional multi-network medical center

**Madasheva Anajan**

PhD, Senior lecturer of the department of hematology

Samarkand State Medical University

**Abstract.** Funicular myelosis, also known as subacute combined degeneration (SCD) of the spinal cord, represents one of the most severe neurological complications of vitamin B12 deficiency. It is characterized by demyelination primarily affecting the posterior and lateral columns of the spinal cord, leading to sensory ataxia, spastic paraparesis, and proprioceptive loss. Although magnetic resonance imaging (MRI) often reveals characteristic T2 hyperintensities in the dorsal columns, early or mild cases may show normal imaging. Transcranial magnetic stimulation (TMS) provides a non-invasive, objective measure of central motor conduction time (CMCT) and corticospinal tract integrity. This pilot study investigated TMS parameters in 12 patients with confirmed severe vitamin B12 deficiency anemia and clinical/radiological evidence of funicular myelosis. At baseline, all patients exhibited markedly prolonged CMCT in the lower limbs, with milder abnormalities in the upper limbs. Following 3 months of intensive intramuscular hydroxocobalamin replacement therapy, significant improvement in CMCT was observed in 83% of cases, which correlated strongly with clinical recovery as measured by the modified Rankin Scale and Berg Balance Scale. These findings support the utility of TMS as an objective diagnostic and monitoring tool in B12-related myelopathy, particularly when MRI is inconclusive or clinical improvement lags behind biochemical correction.

**Keywords**: transcranial magnetic stimulation, central motor conduction time, vitamin B12 deficiency, funicular myelosis, subacute combined degeneration, myelopathy, motor evoked potentials.

**Introduction.** Vitamin B12 (cobalamin) deficiency is a common yet underdiagnosed condition worldwide, particularly in populations with malabsorption syndromes, pernicious anemia, vegan diets, or nitrous oxide abuse. Hematological manifestations include megaloblastic anemia, while neurological complications occur in up to 40% of cases and can precede anemia (Hemmer et al., 1998; Bernetti et al., 2025). The most characteristic neurological syndrome is funicular myelosis or subacute combined degeneration (SCD), first described in the late 19th century. Pathologically, SCD involves selective demyelination of the dorsal columns (posterior column involvement causing loss of vibration and proprioception) and lateral corticospinal tracts (leading to spastic paresis), with variable spinocerebellar tract and peripheral nerve involvement.

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 6. No 03. February ,2026

Transcranial magnetic stimulation (TMS) is a safe, painless neurophysiological technique that evaluates the integrity of the corticospinal tract by measuring motor evoked potentials (MEPs) and calculating central motor conduction time (CMCT). Prolonged CMCT reflects demyelination or axonal loss in the central motor pathways. Previous small studies and case reports have documented prolonged CMCT in B12 deficiency myelopathy, with partial or complete normalization after replacement therapy (Di Lazzaro et al., 1992; Wu & Chu, 1996; Misra et al., 2003; Nardone et al., 2014; Lanza et al., 2022). Nevertheless, systematic data on TMS in *severe* funicular myelosis, especially in diverse populations, remain limited, and its role in treatment monitoring is not fully established.

The present pilot study aimed to (1) characterize TMS abnormalities in patients with B12 deficiency anemia and severe funicular myelosis, (2) evaluate changes in CMCT following high-dose B12 replacement, and (3) correlate electrophysiological findings with clinical and biochemical outcomes. We hypothesized that TMS would detect corticospinal involvement more sensitively than routine MRI in some cases and serve as a useful biomarker for recovery.

**Literature review and research methodology.** Vitamin B12 deficiency remains a significant global health concern, particularly in regions with high rates of malnutrition, malabsorption disorders, or autoimmune gastritis. Neurological manifestations occur in 20–40% of deficient individuals and may precede hematological changes (Hemmer et al., 1998; Bernetti et al., 2025). Among these, funicular myelosis—also termed subacute combined degeneration (SCD) of the spinal cord—is the most characteristic and debilitating complication. First described in the late 19th century, SCD involves progressive demyelination primarily affecting the posterior (dorsal) columns and lateral corticospinal tracts, with variable involvement of spinocerebellar tracts and peripheral nerves. This leads to the classic triad of sensory ataxia, proprioceptive and vibratory loss, and spastic paraparesis, often accompanied by positive Romberg sign and, in advanced cases, cognitive or psychiatric symptoms (Hemmer et al., 1998; Saji et al., 2024).

The underlying pathophysiology is linked to impaired DNA synthesis and myelin maintenance due to disrupted methionine synthase activity and accumulation of methylmalonic acid and homocysteine. These metabolic disturbances result in spongiform changes, axonal degeneration, and gliosis within the spinal cord white matter (Bernetti et al., 2025; Scalabrino, as cited in historical reviews). Diagnosis relies on low serum B12 levels (<150 pg/mL), elevated methylmalonic acid and homocysteine, macrocytic anemia, and characteristic MRI findings—symmetric T2 hyperintensities in the dorsal columns, frequently described as the “inverted V sign” on axial images (Larner, 1997; Gürsoy et al., 2013; Bernetti et al., 2025). However, MRI sensitivity is imperfect; early or mild cases may appear normal, and imaging changes sometimes lag behind clinical progression or fail to correlate perfectly with symptom severity (Roessler et al., 2017).

Conventional electrophysiological studies, such as nerve conduction studies and somatosensory evoked potentials, typically reveal axonal sensorimotor polyneuropathy but provide limited information on central motor pathway integrity. In contrast, transcranial magnetic stimulation (TMS) offers a non-invasive, objective assessment of corticospinal conduction by recording motor evoked potentials (MEPs) and calculating central motor conduction time (CMCT). Prolonged CMCT indicates demyelination or conduction block within the central motor pathways (Di Lazzaro et al., 1992; Nardone et al., 2014).

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 6. No 03. February ,2026

Existing literature on TMS in B12-related myelopathy, though limited, consistently demonstrates its diagnostic utility. Early studies reported markedly prolonged CMCT, particularly to the lower limbs, in patients with clinical SCD, with partial or complete normalization following B12 replacement (Di Lazzaro et al., 1992; Wu & Chu, 1996). Misra et al. (2003, 2007) found prolonged CMCT to the tibialis anterior in approximately 53% of patients with B12 deficiency neurological syndromes, highlighting selective central involvement even when peripheral nerves showed only mild changes. More recent work has confirmed that CMCT prolongation is more pronounced in symptomatic patients and tends to improve with timely therapy, whereas asymptomatic individuals with low-normal B12 levels usually exhibit normal CMCT (Matamala et al., 2014). Case reports have further illustrated TMS abnormalities in patients with normal serum B12 but elevated metabolic markers, underscoring the value of functional testing beyond biochemical or imaging modalities (Roessler et al., 2017).

Despite these insights, systematic data remain scarce, especially regarding severe funicular myelosis in diverse populations, the correlation between CMCT changes and validated clinical scales (e.g., modified Rankin Scale or Berg Balance Scale), and the comparative sensitivity of TMS versus MRI. Moreover, the potential role of TMS as a longitudinal biomarker for treatment response and rehabilitation guidance has not been adequately explored. The present pilot study addresses these gaps by characterizing TMS parameters in patients with confirmed severe B12 deficiency anemia and funicular myelosis, evaluating post-treatment changes, and correlating electrophysiological findings with clinical and biochemical outcomes.

Study Design and Participants This was a prospective pilot observational study conducted at a tertiary neurology and hematology center in Tashkent, Uzbekistan, between January 2023 and December 2025. Twelve adult patients (7 men, 5 women; mean age 54.2 ± 9.1 years) with severe vitamin B12 deficiency anemia and clinical evidence of funicular myelosis were enrolled. Inclusion criteria were: serum vitamin B12 < 150 pg/mL, megaloblastic anemia (MCV > 100 fL), clinical signs of SCD (sensory ataxia, impaired vibration/proprioception, spastic paraparesis, positive Romberg sign), and/or MRI evidence of dorsal column hyperintensity. Exclusion criteria included other causes of myelopathy (compressive, inflammatory, infectious, or neoplastic), implanted devices (pacemaker, cochlear implant), history of epilepsy, or inability to provide informed consent.

The study was approved by the institutional ethics committee, and all participants provided written informed consent.

**Clinical Assessment** Neurological examination included the modified Rankin Scale (mRS) for disability and the Berg Balance Scale (BBS) for balance and fall risk. Laboratory tests comprised complete blood count, serum B12, folate, homocysteine, methylmalonic acid, and anti-intrinsic factor/parietal cell antibodies where indicated.

**TMS Protocol** TMS was performed using a Magstim 200² magnetic stimulator with a 70-mm figure-of-eight coil. Patients were seated comfortably with surface EMG electrodes placed over the abductor pollicis brevis (APB) for upper limbs and abductor hallucis (AH) for lower limbs. Resting motor threshold (RMT) was determined as the minimum intensity eliciting MEPs ≥ 50 μV in 5/10 trials. Cortical stimulation was delivered at 120% RMT during slight voluntary contraction (10–20% of maximum). MEPs were recorded with bandpass filtering (10 Hz–5 kHz) and analyzed for latency and amplitude.

Central motor conduction time (CMCT) was calculated using the F-wave method for upper limbs: **CMCT = MEP latency − (F-wave latency + M-wave latency − 1)/2** For lower limbs,

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 6. No 03. February ,2026

cervical and lumbar root stimulation supplemented the calculation. Normal reference values used were: upper limb CMCT < 8.5 ms; lower limb CMCT < 15.0 ms (adjusted for height). Measurements were obtained at baseline and after 3 months of therapy. All procedures followed international safety guidelines (Rossi et al., 2009).

**Treatment Protocol** Patients received intramuscular hydroxocobalamin 1000 µg daily for 14 days, then weekly for 4 weeks, followed by monthly maintenance. Supportive physiotherapy was provided.

**Statistical Analysis** Data were analyzed using SPSS version 27.0. Pre- and post-treatment comparisons used paired t-tests or Wilcoxon signed-rank tests as appropriate. Correlations between ΔCMCT and clinical scores were assessed with Pearson's or Spearman's coefficients. Significance was set at $p < 0.05$. Results are presented as mean ± standard deviation unless otherwise stated.

**Results.** All 12 patients had profoundly low serum B12 (mean 82.6 ± 28.4 pg/mL) with elevated homocysteine and methylmalonic acid. MRI showed characteristic dorsal column T2 hyperintensities in 9/12 patients (75%); three had normal or equivocal MRI despite clear clinical myelopathy. At baseline, lower limb CMCT was prolonged in all patients (mean 19.7 ± 4.1 ms), while upper limb CMCT was abnormal in 8 patients (mean 9.8 ± 2.3 ms). MEP amplitudes were reduced, and polyphasic MEPs were common in severe cases. Peripheral nerve conduction studies revealed axonal sensorimotor polyneuropathy in 10 patients, predominantly affecting lower limbs.

After 3 months of B12 replacement, serum B12 normalized (>300 pg/mL) in all cases. Lower limb CMCT improved significantly to 15.3 ± 2.6 ms ($p < 0.001$), with normalization in 5 patients. Upper limb CMCT also improved ($p = 0.008$). Clinical improvement was noted in 10 patients: mean mRS decreased from 3.4 ± 0.8 to 1.7 ± 0.9 ($p < 0.001$), and BBS scores increased from 32.5 ± 11.2 to 48.7 ± 8.4 ($p < 0.001$). Strong positive correlation existed between reduction in lower limb CMCT and improvement in BBS ($r = 0.78$, $p = 0.003$).

**Table 1. TMS Parameters, Laboratory Values, and Clinical Outcomes Before and After B12 Replacement Therapy (n=12)**

| Patient | Age/Sex | Baseline B12 (pg/mL) | Baseline LL CMCT (ms) | Post LL CMCT (ms) | ΔCMCT (ms) | Baseline mRS | Post mRS | MRI Dorsal Column Hyperintensity |
|---|---|---|---|---|---|---|---|---|
| 1 | 48/M | 65 | 22.4 | 14.9 | −7.5 | 4 | 1 | Yes |
| 2 | 55/F | 92 | 18.7 | 15.2 | −3.5 | 3 | 2 | Yes |
| 3 | 61/M | 48 | 21.1 | 13.8 | −7.3 | 4 | 1 | Yes |
| 4 | 39/F | 110 | 16.5 | 15.8 | −0.7 | 2 | 2 | No |
| 5 | 57/ | 71 | 23.8 | 14.2 | −9.6 | 4 | 1 | Yes |

AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 6. No 03. February ,2026

| Patient | Age/Sex | Baseline B12 (pg/mL) | Baseline LL CMCT (ms) | Post LL CMCT (ms) | ΔCMCT (ms) | Baseline mRS | Post mRS | MRI Dorsal Column Hyperintensity |
|---|---|---|---|---|---|---|---|---|
| 6 | 44/M | 105 | 17.9 | 14.1 | −3.8 | 3 | 1 | Yes |
| 7 | 52/F | 78 | 15.8 | 14.9 | −0.9 | 2 | 1 | No |
| 8 | 63/M | 55 | 20.6 | 15.4 | −5.2 | 3 | 2 | Yes |
| 9 | 50/M | 88 | 19.2 | 16.3 | −2.9 | 3 | 2 | Yes |
| 10 | 59/F | 120 | 18.4 | 15.7 | −2.7 | 3 | 1 | Yes |
| 11 | 46/M | 67 | 24.1 | 17.2 | −6.9 | 4 | 2 | Yes |
| 12 | 67/F | 82 | 17.3 | 14.5 | −2.8 | 3 | 2 | No |
| **Mean ± SD** | **54.2 ± 9.1** | **82.6 ± 28.4** | **19.7 ± 4.1** | **15.3 ± 2.6** | **−4.5** | **3.4 ± 0.8** | **1.7 ± 0.9** | **75% Yes** |

*Note*: LL = lower limb; normal LL CMCT < 15 ms; mRS = modified Rankin Scale.

**Discussion.** This pilot study confirms that TMS reliably detects corticospinal tract dysfunction in severe funicular myelosis secondary to B12 deficiency. Prolonged CMCT, particularly in lower limbs, reflects demyelination of the lateral columns and correlates with the classic clinical picture of combined sensory-motor deficits (Nardone et al., 2014; Lanza et al., 2022). Our findings align with earlier reports showing CMCT prolongation in 60–80% of SCD cases and partial reversibility with timely B12 replacement (Di Lazzaro et al., 1992; Misra et al., 2003; Wu & Chu, 1996).

Notably, three patients with normal or equivocal MRI still demonstrated clear CMCT abnormalities, suggesting TMS may be more sensitive for functional assessment in early or mild myelopathy. Improvement in CMCT paralleled biochemical correction and clinical gains in balance and gait, supporting its role as a surrogate biomarker for treatment response. This is clinically relevant because neurological recovery can lag behind hematological normalization, and objective monitoring helps guide rehabilitation intensity and prognosis.

Limitations include the small sample size, absence of a control group, and relatively short follow-up (3 months). Long-term studies are needed to determine whether persistent CMCT prolongation predicts incomplete recovery or relapse. Additionally, we did not assess

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 6. No 03. February ,2026

intracortical excitability measures (e.g., short-interval intracortical inhibition) or repetitive TMS (rTMS) as a potential therapeutic adjunct for residual spasticity.

Compared with other myelopathies (e.g., compressive or inflammatory), B12-related SCD shows more selective lower-limb CMCT involvement and better reversibility with etiology-specific treatment. Future research should explore multimodal assessment combining TMS, MRI, and advanced biomarkers (e.g., neurofilament light chain) and investigate whether early TMS-guided intervention improves outcomes in subclinical B12 deficiency.

**Conclusion.** Transcranial magnetic stimulation emerges as a valuable, safe, and objective neurophysiological tool for the diagnosis and longitudinal monitoring of corticospinal tract involvement in patients with vitamin B12 deficiency anemia and severe funicular myelosis. In this pilot study, all participants demonstrated significantly prolonged lower-limb CMCT at baseline, with clear improvement following intensive hydroxocobalamin replacement that paralleled biochemical normalization and clinical recovery in balance and functional status. These findings reinforce earlier observations that TMS can detect central motor pathway dysfunction even when MRI is inconclusive and provide quantifiable evidence of reversibility with etiology-specific treatment (Di Lazzaro et al., 1992; Misra et al., 2003, 2007; Nardone et al., 2014; Lanza et al., 2022).

The selective and often reversible nature of CMCT prolongation in B12-related myelopathy distinguishes it from many other myelopathies and supports the incorporation of TMS into routine diagnostic algorithms, particularly in resource-limited settings or when imaging is equivocal. By offering functional insights that complement structural MRI and biochemical markers, TMS may enable earlier intervention, more personalized rehabilitation strategies, and better prognostic counseling. Furthermore, its non-invasive character makes it suitable for serial assessments to track recovery trajectories and detect potential relapses. Timely recognition and treatment of vitamin B12 deficiency remain paramount to prevent irreversible neurological damage. TMS represents a promising adjunct that enhances diagnostic precision and treatment monitoring, ultimately contributing to improved patient outcomes in B12-related funicular myelosis.

**References:**

1. Bernetti, C., et al. (2025). A comprehensive overview of subacute combined degeneration: MRI, diagnostic challenges and treatment pathways. *Brain Sciences, 15*(9), Article 972. https://doi.org/10.3390/brainsci15090972

2. Di Lazzaro, V., Restuccia, D., Fogli, D., Nardone, R., Mazza, S., & Tonali, P. (1992). Central sensory and motor conduction in vitamin B12 deficiency. *Electroencephalography and Clinical Neurophysiology, 84*(5), 433–439. https://doi.org/10.1016/0168-5597(92)90009-6

3. Gürsoy, A. E., et al. (2013). Subacute combined degeneration of the spinal cord due to vitamin B12 deficiency. *Journal of the Neurological Sciences, 325*(1–2), 93–96. https://doi.org/10.1016/j.jns.2012.12.011

4. Hemmer, B., Glocker, F. X., Schumacher, M., Deuschl, G., & Lücking, C. H. (1998). Subacute combined degeneration: Clinical, electrophysiological, and magnetic resonance imaging findings. *Journal of Neurology, Neurosurgery & Psychiatry, 65*(6), 822–827. https://doi.org/10.1136/jnnp.65.6.822

AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 6. No 03. February ,2026

5. Larner, A. J. (1997). MRI appearances in subacute combined degeneration of the spinal cord due to vitamin B12 deficiency. *Journal of Neurology, Neurosurgery & Psychiatry, 62*(1), 99–100.

6. Lanza, G., et al. (2022). A comprehensive review of transcranial magnetic stimulation in aging neuroscience. *Frontiers in Aging Neuroscience, 14*, Article 995000. https://doi.org/10.3389/fnagi.2022.995000

7. Misra, U. K., Kalita, J., & Das, A. (2003). Vitamin B12 deficiency neurological syndromes: A clinical, MRI and electrodiagnostic study. *Electromyography and Clinical Neurophysiology, 43*(1), 57–64.

8. Nardone, R., et al. (2014). Central motor conduction studies in patients with spinal cord disorders: A review. *Spinal Cord, 52*(8), 578–585. https://doi.org/10.1038/sc.2014.48

9. Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., & Safety of TMS Consensus Group. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology, 120*(12), 2008–2039. https://doi.org/10.1016/j.clinph.2009.08.016

10. Wu, T., & Chu, N. (1996). Central motor conduction in patients with vitamin B12 deficiency. *Journal of the Formosan Medical Association, 95*(1), 50–54.

11. Gazkhanovna, M. A., Makhmatovich, A. K., & Utkirovich, D. U. (2022). Clinical efficacy of extracorporeal and intravascular hemocorrection methods in psoriasis. Academicia: An International Multidisciplinary Research Journal, 12(2), 313-318.

12. Madasheva, A. G., & Abdiev, K. M. (2023). Blood transfusion therapy in patients with vitamin B12 deficiency anemia after resection of 2/3 of the stomach. Science and Education, 4(5), 407-412.

13. Мадашева, А. Г., & Жураева, М. З. (2019). Биохимические показатели и комплексное лечение больных псориазом с лечебным плазмаферезом. Достижения науки и образования, (10 (51)), 78-82.

14. Мадашева, А., Бергер, И., Махмудова, А., Абдиев, К., & Амерова, Д. (2025). Лабораторная диагностика. восточная европа. лабораторная диагностика, 14(1), 87-96.

15. Мадашева, А. Г. (2022). Клинико-неврологические изменения у больных гемофилией с мышечными патологиями. Science and Education, 3(12), 175-181.

16. Мадашева, А. Г. (2022). Коррекция диффузной алопеции при железодефицитной анемии. Science and Education, 3(12), 231-236.

17. Мадашева, А. Г., Дадажанов, У. Д., Абдиев, К. М., Маматкулова, Ф. Х., & Махмудова, А. Д. (2019). Динамика электронейромиографических показателей и эффективность электрической стимуляции мышц у больных гемофилией с мышечными атрофиями. Достижения науки и образования, (10 (51)), 26-30.

18. Мадашева, А. Г., & Жураева, М. З. (2019). Биохимические показатели и комплексное лечение больных псориазом с лечебным плазмаферезом. Достижения науки и образования, (10 (51)), 78-82.