

Short Communication

# Diagnostic and prognostic value of Transcranial Magnetic Stimulation in mucopolysaccharidosis-related cervical myelopathy

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**Abstract:** Background: Cervical myelopathy (CM) is a common cause of morbidity and disability in patients with mucopolysaccharidosis (MPS) and, therefore, early detection is crucial for best surgical intervention and follow-up. Transcranial Magnetic Stimulation (TMS) non-invasively evaluates the conductivity along the cortico-spinal tract, also allowing preclinical diagnosis and monitoring. Methods: motor evoked potentials (MEPs) to TMS were recorded in a group of 8 patients with MPS-related CM. Responses were obtained during mild tonic contraction through a circular coil applied over the “hot spot” of the first dorsal interosseous and tibialis anterior muscles, bilaterally. Central motor conduction time was estimated as the difference between MEP cortical latency and the peripheral motor conduction time by cervical or lumbar magnetic stimulation. Peak-to-peak MEP amplitude to cortical stimulation and right-to-left difference of each parameter were also measured. Results: TMS revealed abnormal findings from both upper and lower limbs compatible with axonal damage and demyelination in 6 of them. Notably, a subclinical cervical spinal disease was detected before the occurrence of an overt CM in two patients, whereas TMS signs compatible with a CM of variable degree persisted despite surgery in all treated subjects. Conclusions: TMS screening should be performed in MPS patients, before and after surgery.

**Keywords:** motor evoked potentials lysosomal disorders; cortical-spinal tract; spinal cord compression; cervical myelopathy; clinical neurophysiology.

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## 1. Introduction

Mucopolysaccharidosis (MPS) are a group of rare, inherited lysosomal disorders due to defective catabolism and storage of glycosaminoglycans (GAG) in the skeleton and soft tissues. MPS encompass a wide and heterogeneous spectrum of clinical manifestations and severity, which ranges from severe to very mild phenotypes that may be recognized only in adulthood. Common clinical presentation includes growth retardation, short stature, visceromegaly, typical facial features,

macrocephaly, macroglossia, and cardiac and skeletal abnormalities, with multiple dysostosis [1]. Primary central nervous system (CNS) involvement causing cognitive regression and behavioral disturbances occurs in patients with neuronopathic MPS type I, II, III, and VII [2].

Cervical cord compression is most frequently observed in MPS I, II, IV, and VI. In particular, cervical myelopathy (CM) is the main cause of neurological morbidity and disability in MPS [3] and negatively impacts the course and the quality of life of these patients [4]. CM results from spinal canal stenosis, which generally develops due to thickening of connective tissues (dura mater and ligaments) surrounding the spinal canal, secondary to GAG accumulation and fibrosis, epidural lipomatosis, and/or degeneration of vertebral bodies. Atlanto-axial subluxation due to odontoid hypoplasia may contribute to spinal cord compression and related clinical manifestations.

Enzyme replacement therapy (ERT) is now available for MPS I, II, IVA, VI, and VII. Although the effectiveness of ERT has been proven on different systemic complications of MPS, thus improving the lifespan of these patients, it does not have effect on CM [5]. Given that an early detection of CM is associated with the best surgical outcome and post-operative course, both an accurate diagnosis and a strict monitoring are recommended [6].

Magnetic resonance imaging (MRI) and computed tomography are the methods of choice to display spinal cord compression and vertebral abnormalities, respectively, although they do not provide any information on the functional status. In this context, motor evoked potentials (MEPs) to Transcranial Magnetic Stimulation (TMS) are widely employed in daily clinical practice to non-invasively estimate *in vivo* and in real time the excitability and conductivity of the cortico-spinal tract [7], also allowing a preclinical diagnosis and monitoring [8-12]. In particular, MEP latency and central motor conduction time (CMCT) are considered as reliable indexes of the integrity of the cortical-spinal myelination, whereas the MEP amplitude is used to measure the excitation state of the neuronal axons connecting the motor cortex to the spinal motoneurons till the muscles [7].

While several and robust TMS evidences are available in patients with different neurological disorders affecting the central motor system, to date few neurophysiological studies have been carried out in MPS-related CM [13-17]. Here, we applied TMS in patients with MPS to detect any electrophysiological sign, even at a subclinical level, of CM.

## 2. Materials and Methods

Eight patients (two males; median age 14.5 years, range 13.0-41.0) with a clinical, biochemical, and genetic diagnosis of MPS [18] were consecutively recruited from the "Referral Center for Inherited Metabolic Diseases, Department of Clinical and Experimental Medicine" of the University of Catania, Italy. Among these subjects, six (patient 1-6) had MPS IVA (Morquio disease, type A), whereas the remaining two (patient 7 and 8) had MPS VI (Maroteaux-Lamy syndrome).

As shown in Table 1, six subjects (1-4, 7, and 8) had previously received surgical decompression due to clinical and MRI evidence of CM, although four of them (1, 3, 7, and 8) still complained neurological deficits. Regardless of previous surgery, at the time of the study, four patients with MPS IVA (2, 4, 5, and 6) did not have radiological evidences of CM. Finally, the two subjects with MPS VI had been treated with ERT for three years.

The study was conducted in accordance with the Declaration of Helsinki and all participants (or parents) gave their informed consent for inclusion before they participated in the study. This investigation was part of a larger multi-center study on clinical and molecular characterization of patients with MPS and was approved by the Ethics Committee of the "Azienda Ospedaliero-Universitaria Policlinico – Vittorio Emanuele" of Catania, Italy (PRIN 2012 code 20122EK9SZ\_005).

**Table 1.** Clinical-demographic features of MPS patients at the time of the study.

| Patient                          | 1     | 2     | 3     | 4      | 5    | 6    | 7      | 8      |
|----------------------------------|-------|-------|-------|--------|------|------|--------|--------|
| MPS type                         | IVA   | IVA   | IVA   | IVA    | IVA  | IVA  | VI     | VI     |
| Sex/age (years)                  | F/14  | M/15  | F/16  | M/13   | F/20 | F/40 | F/13   | F/14   |
| ERT (age, years)                 | -     | -     | -     | -      | -    | -    | + (9)  | + (10) |
| Height (cm)                      | 98    | 100   | 102   | 110    | 150  | 113  | 120    | 110    |
| Spinal cord surgery (age, years) | + (5) | + (4) | + (8) | + (10) | -    | -    | + (10) | + (11) |
| Diffuse brisk tendon reflex      | +     | -     | +     | +      | -    | -    | +      | +      |
| Limbs paresis/weakness           | +     | -     | +     | -      | -    | -    | +      | +      |
| Walking assistance               | +     | -     | +     | -      | -    | -    | -      | +      |
| MRI cervical cord compression    | +     | +     | +     | +      | -    | -    | +      | +      |
| MRI cervical myelopathy          | +     | -     | +     | -      | -    | -    | -      | +      |

MPS = mucopolysaccharidosis; F = female; M = male; ERT = enzyme replacement therapy; MRI = magnetic resonance imaging; + = present; - = absent.

MEPs to TMS is included within the conventional diagnostic work-up of patients with suspected or overt CM, as well as in the peri- and post-operative course [7].

A high-power monopulse electromagnetic stimulator MagStim 220 (The Magstim Co., Ltd., Whitland, Dyfed, United Kingdom) connected to a 90 mm circular coil (inner diameter of 5 cm), routinely employed for diagnostic TMS was used to evoke motor responses. A standard examination involves bilateral recordings from distal limb muscles while the patient is seated or lying on an armchair. MEPs were recorded via standard surface EMG silver/silver chloride cup electrodes (9 mm diameter), filled with electrode jelly and applied on the First Dorsal Interosseous (FDI) and Tibialis Anterior (TA) muscles contralaterally to the side of stimulation, in a conventional belly tendon montage [7].

Coil was applied with the handle pointing backward and held tangentially flat on the scalp, with its center positioned over Cz (according to the international EEG 10-20 system) for recording from the FDI muscle and over Fz for recording from the TA muscle. First, a reference MEP to TMS in the relaxed muscle was obtained. Then, subjects were asked to produce a small transient tonic contraction (about 10–20% of the subject's maximum voluntary contraction, just enough to overcome gravity), in order to obtain MEPs with higher amplitude and shorter latency compared to the reference response. The MEP with the shortest latency was considered for CMCT calculation, according to international guidelines. Likewise, since diagnostic TMS estimates the cortico-motor response with maximal amplitude, only the trial with the largest peak-to-peak amplitude was used for MEP size analysis. Peripheral stimulation of the motor roots was carried out in all subjects to determine peripheral motor conduction time (PMCT). The center of the coil was placed posteriorly over the 7<sup>th</sup> cervical (for upper limbs) and 4<sup>th</sup> lumbar (for lower limbs) spinous process. CMCT was defined as the conduction time from motor cortical neurons to spinal motor neurons, thus reflecting the conductivity along the cortico-spinal tract (from the upper to the lower motor neuron). CMCT was estimated by subtracting the peripheral (cervical or lumbar) PMCT from the shortest MEP cortical latency [7].

All motor responses were obtained at 80% of the maximum stimulator output, based on the evidence that threshold stimulation for a 2.0 Tesla magnetic stimulator is about 50–65% of the maximal output [19–21]. Motor responses were amplified and filtered (bandwidth 3–3,000 Hz) using a 2-channel Medelec Synergy system (Oxford Instruments Medical, Inc., United Kingdom).

**Table 2.** Motor evoked potentials of MPS patients.

| N. | First Dorsal Interosseous muscle |            |      |                          |   |                      |           |      |              |             |      | Tibialis Anterior muscle |            |      |                      |           |      |              |        |      |
|----|----------------------------------|------------|------|--------------------------|---|----------------------|-----------|------|--------------|-------------|------|--------------------------|------------|------|----------------------|-----------|------|--------------|--------|------|
|    | MEPs<br>amp (mV)                 |            | ID   | Poly-<br>phasic<br>shape |   | MEPs<br>latency (ms) |           | ID   | CMCT<br>(ms) |             | ID   | MEPs<br>amp (mV)         |            | ID   | MEPs<br>latency (ms) |           | ID   | CMCT<br>(ms) |        | ID   |
|    | R                                | L          |      | R                        | L | R                    | L         |      | R            | L           |      | R                        | L          |      | R                    | L         |      | R            | L      |      |
|    | > 2.8                            | > 2.8      | <4.0 | -                        | - | <                    | <         | <1.5 | <7.6         | <7.6        | <1.5 | >1.9                     | >1.9       | <4.0 | <                    | <         | <4.1 | < 17.2       | < 17.2 | <3.0 |
|    |                                  |            |      |                          |   | 22.5                 | 22.5      |      |              |             |      |                          |            |      | 31.2                 | 31.2      |      |              |        |      |
| 1  | <b>0.2</b>                       | <b>0.1</b> | 0.1  | +                        | + | 19.2                 | 20.0      | 0.8  | na           | <b>10.1</b> | /    | <b>0.3</b>               | <b>nr</b>  | /    | 29.3                 | <b>nr</b> | /    | <b>21.2</b>  | na     | /    |
| 2  | <b>2.6</b>                       | <b>2.2</b> | 0.4  | -                        | + | 16.5                 | 17.1      | 0.6  | <b>8.1</b>   | <b>8.1</b>  | 0.0  | 3.2                      | <b>1.7</b> | 1.5  | 19.6                 | 21.5      | 1.9  | 12.3         | 14.0   | 1.7  |
| 3  | <b>0.3</b>                       | <b>0.2</b> | 0.1  | +                        | + | 19.4                 | 20.6      | 1.2  | na           | na          | /    | <b>nr</b>                | <b>nr</b>  | /    | <b>nr</b>            | <b>nr</b> | /    | na           | na     | /    |
| 4  | <b>0.8</b>                       | <b>0.6</b> | 0.2  | +                        | + | 17.3                 | 17.2      | 0.1  | <b>9.6</b>   | <b>9.4</b>  | 0.2  | 2.9                      | 2.5        | 0.4  | 18.5                 | 19.8      | 1.3  | 12.5         | 12.6   | 0.1  |
| 5  | 8.0                              | 7.0        | 1.0  | -                        | - | 17.4                 | 16.2      | 1.2  | 5.4          | 6.0         | 0.6  | 7.0                      | 6.0        | 1.0  | 20.0                 | 19.5      | 0.5  | 11.6         | 11.6   | 0.0  |
| 6  | 3.8                              | 3.5        | 0.3  | -                        | - | 18.3                 | 18.5      | 0.2  | 6.1          | 6.4         | 0.3  | 3.0                      | 4.0        | 1.0  | 24.9                 | 25.2      | 0.3  | 14.7         | 14.3   | 0.4  |
| 7  | <b>nr</b>                        | <b>nr</b>  | /    | /                        | / | <b>nr</b>            | <b>nr</b> | /    | na           | na          | /    | <b>nr</b>                | <b>nr</b>  | /    | <b>nr</b>            | <b>nr</b> | /    | na           | na     | /    |
| 8  | <b>nr</b>                        | <b>nr</b>  | /    | /                        | / | <b>nr</b>            | <b>nr</b> | /    | na           | na          | /    | <b>nr</b>                | <b>nr</b>  | /    | <b>nr</b>            | <b>nr</b> | /    | na           | na     | /    |

MPS = mucopolysaccharidosys; N. = patient number; MEPs = motor evoked potentials; R = right; L = left; rv = reference values; ID = interside difference; - = absent; + = present; amp = amplitude; CMCT = central motor conduction time; nr: not recordable; na = not available due to absence of the evoked response by cervical or lumbar nerve root magnetic stimulation; numbers in italics = reference values [22]; numbers in bold = pathological values.

### 3. Results

Table 2 summarizes the patients' neurophysiological features. Overall, TMS was well tolerated and no side-effect or significant discomfort was reported during or after the exam.

Among those who had undergone surgery for CM (patient 1-4, 7, and 8), MEPs were bilaterally absent from FDI and TA muscles in both patients with MPS VI (7 and 8), who already had a neurological impairment before treatment. In the treated patients with MPS IVA (1-4), MEPs were bilaterally absent from TA muscle in patient 3 as well as from the left TA muscle of patient 1. In the same patients (1-4), MEPs also showed reduced amplitude and polyphasic shape. Overall, CMCT was increased in three of the treated subjects from upper limbs (1, 2, and 4), whereas responses to cervical root stimulation could not be evoked in other three (3, 7, and 8).

Among the four subjects without overt neurological symptoms (2, 4, 5, and 6), MEPs were abnormal in terms of reduced amplitude, increased latency, or polyphasic shape in at least one of the examined muscles in two of them (patient 2 and 4), whereas they were entirely normal in the other two (patient 5 and 6).

CMCT could not be bilaterally assessed at four limbs in three patients (3, 7, and 8) due to the absence of the evoked response by cervical or lumbar nerve root magnetic stimulation. Finally, no significant right-to-left difference was found for any of the TMS variable considered.

### 4. Discussion

In the present study, we found abnormal TMS findings from upper and/or lower limbs in 6 out of 8 MPS patients, consistent with both diffuse axonal damage and demyelination. This suggests that a cervical spinal disease was clinically present before the occurrence of an overt CM and persisted, with a different clinical and neurophysiological level of severity, despite surgery. In this context, it should be acknowledged that patients with MPS may suffer from a wide spectrum of neurological symptoms that involves the CNS and the peripheral nerves and the musculo-skeletal system. In particular, they usually need neurosurgical intervention for CM or vertebro-spinal anomalies, although a spinal cord compression may occur and progress even in the absence of overt neurological symptoms [23].

Notably, MEPs response were bilaterally absent at four limbs from the two patients with MPS VI. This finding is compatible with a severe CM-related involvement of the cortico-spinal tract and suggests that this MPS type is particularly associated with an early-onset CM and related complications. Accordingly, recent recommendations from the "MPS VI Clinical Surveillance Program" conclude that all individuals with MPS VI are at high risk of developing CM at an early age and that MRI monitoring should be performed from the time of MPS VI diagnosis [24]. Moreover, the peri-operative management of MPS VI patients is often challenging and, therefore, the electrophysiological studies play a significant role in providing both surgical indication and proper timing, as well as in the monitoring of post-operative course.

MEPs analysis also revealed a functional impairment even in two patients without a clear evidence of CM, thus allowing a preclinical diagnosis [13]. Therefore, TMS can be viewed as an extension of clinical examination and the functional counterpart of the neuroimaging techniques in assessing spinal cord disease, including the very early stages.

To date, the role of electrophysiological studies in detecting compressive myelopathy in patients with MPS was investigated by few previous reports [13-15], and one study only has used TMS for the evaluation of the post-operative follow-up in a single patient with MPS VI [16]. In this frame, the intraoperative neurophysiological monitoring by using MEPs and somatosensory evoked potentials seems to be of pivotal interest as it provides relevant functional information during surgical procedures [17]. Anyhow, since cervical cord compression in MPS is progressive and may produce rapid loss of sensory-motor functions in these patients (especially in those with type VI), surgery is indicated as soon a myelopathy is detected, even subclinically, as severely myelopathic subjects show little or no recovery after the operation [14,25], also at the TMS level, as confirmed by the present investigation.

It is worth to mention that histological examination in a mice model of MPS type I showed storage of GAG in the cortex and cerebellum, along with the evidence of a progressive inflammatory response that can contribute to the neurological deficit [26]. Based on its intrinsic properties, TMS might be considered as an additional tool able to disclose subclinical CNS involvement related to a neuroinflammatory status in MPS, a finding which has been also demonstrated in other metabolic disorders [27-29]. In this view, innovative neuromodulatory protocols based on non-invasive brain stimulation techniques might be applied to transiently modulate cortical excitability, synaptic plasticity, and functional connectivity [30-32].

The main limitation of this study is the small sample size, although MPS are rare disorders. Another caveat is that only patients with severe MPS VI phenotype were included, thus we cannot compare these findings with those from patients with mild phenotype.

## 5. Conclusions

TMS was able to detect MPS-associated CM, even subclinically, and to provide useful electrophysiological data after surgical decompression. These findings suggest that MEP screening for CM should be performed in all MPS patients. Further studies and longitudinal exams are needed for early diagnosis, accurate prognosis, and adequate monitoring.

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