Upper limb motor evoked potentials as a motor outcome in progressive MS

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Introduction and Purpose

Clinical trials on disease-modifying drugs in people with progressive MS (PMS) have been often less promising than expected. The use of outcome measures focusing on nervous pathways with exhausted functional reserve, as lower limb (LL) motor function, may have limited these results, as from better results in upper limb (UL) function in recent trials.
We investigated the value of motor evoked potentials (MEPs) to the upper and lower limbs as motor outcome in people with PMS.

Methods

People with PMS (n=40) with predominant pyramidal involvement (EDSS 4.0-6.5; P>3, C<2) and impaired ambulation (10 meter walk test-10MWT ranging from 10 seconds to 1 minute) underwent clinical motor measures to the upper (9 hole peg test–9HPT) and lower limb (MS walking scale-MSWS, 6 minutes walk test-6MWT, 10MWT), MRC (5 muscles for UL and 7 for LL), MAS (3 per limb). Neurophysiological measures consisted in resting MEPs to the tibialis anterior bilaterally and to the right first dorsal interosseous, with assessment of resting motor threshold-RMT, latency and amplitude of MEPs at 120% of RMT.

Results

Upper limb assessment:

Strength was measured using Medical Research Council (*MRC*) scale, ranging from 0 to 5, on 5 muscles for each limb. In our cohort 55.6% had normal strength (25/25) considering separately right and left UL. Mean MRC score in right UL was 22.2 ± 5.4, in left UL was 23.2 ± 2.2. 33.3% of patients had bilateral UL weakness while 44.4% had bilateral normal strength.

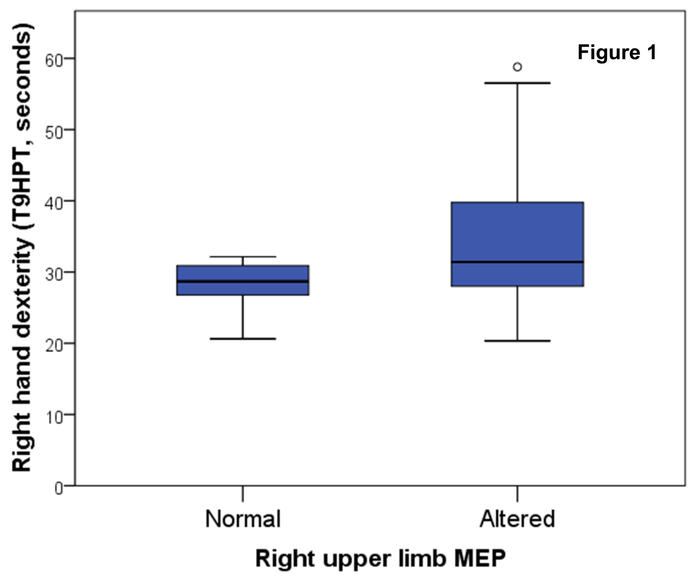
Spasticity: Modified Ashworth Scale (*MAS*, ranging 0 to 4) on 3 joints per limb. Less then 5% of our cohort presented increase in muscles tone (right UL: 5.1% with MAS > 0, mean 0.22; left UL: 2.6%, mean 0.13) and 94.9% had bilateral normal tone.

Dexterity: 9 hole peg test (*9HPT*). Only 13,5% had normal dexterity while the 27% had a severe bilateral hand dysfunction (cut-off values 23.03 and 33.3 sec; Feys 2017). Mean time to complete 9HPT was 32.53 sec. for the right hand and 35.83 for the left hand.
The 35% of our patients had normal strength but mild dexterity impairment at 9HPT test.

		Dexterity impairment (9HPT)			
		normal	mild impairment	severe impairment	
UL strenght MRC (0-25)	hyposthenic	2 3.9%	6 11.8%	13 25.5%	21 41.2%
	normal	7 13.7%	18 35.3%	5 9.8%	30 58.8%
		9 17.6%	24 47.1%	18 35.3%	51 100,0%

Measures of dexterity, weakness and tone correlated one another. MRC and 9HPT: Spearman rho -0.436 (p = 0,001). MAS and MRC Spearman rho -0.413 (p = 0,002). 9HPT and MAS Spearman rho 0.256 (p = 0,026).

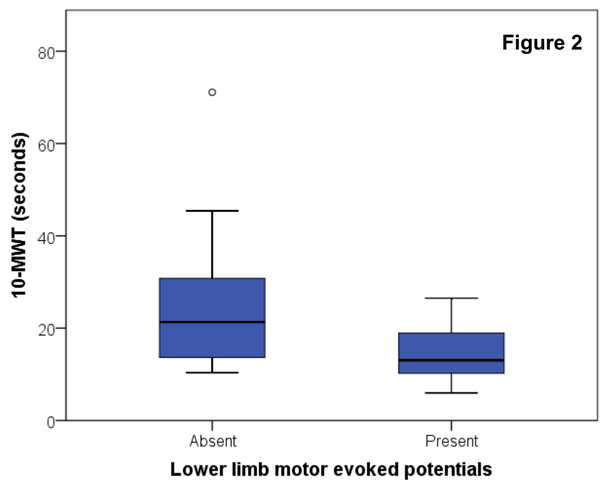
UL MEP. MEPs to the right dorsal interosseous were absent in 12.5% patients and 82.9% of evoked MEP had increased latency. Abnormal UL MEP were associated with dexterity impairment at the 9HPT (Kendal's tau: 0.338; p = 0,008) with significantly higher times to complete the 9HPT in patients with abnormal UL MEP compared with normal MEP (27.8 vs 34 sec; T-test p = 0,014) **Figure 1**.
No association was found between neurophysiological measures and MAS or MRC scales.

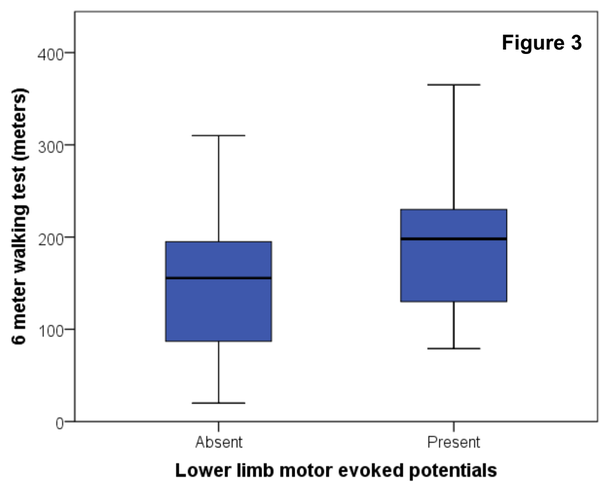


Lower limb assessment:

All patients had ambulatory impairment as inclusion criteria for the study. Mean 6MWT was 175 ± 87 meter and mean time to complete 10MWT (average between two consecutive tests) 10.49 ± 12.35 seconds.
MAS was test on 3 joints, mean value was 3.83 ± 3.21 and 82% had an increase in muscular tone. All patients displayed lower limb weakness, defined as a reduction of at least 1 point of MRC scale in at least one among 7 muscles tested per limb (therefore global MRC < 70) and mean MRC score at lower limb was 59 ± 6.

MEPs to the lower limb (tibialis anterior) were absent bilaterally in 57.5% of patients, evoked MEP were delayed in 37.5% of limbs. Absence of evoked MEPs at both limbs was significantly associated with higher 10MWT (25.08 + 14 SD vs 14.53 + 5.97 SD sec; p=0.003; **Figure 2**) and lower 6MWT (152.5 + 82.7 SD vs 204.9 + 86.35 SD mt; p=0.053; **Figure 3**). MEPs amplitude was significantly correlated with 6MWT (rho 0.745; p=0.013) and MSWS (rho -0.656; p=0.039).





Absence of LL MEP was associated with higher UL RMT (62.5% + 12 SD vs 53% + 11.6 SD sec; p=0.036) and UL MEP latency (29.3 + 4 SD vs 24.5 + 2.2 SD sec; p<0.001). Subjects with abnormal UL MEPs had significantly worse 10MWT (22.39 + 12.9 SD vs 11.76 + 1.11 SD sec; p=0.011) and a trend to lower 6MWT (221.1 + 50 SD vs 165.31 + 90.9 SD mt; p=0.053).

Conclusions

Clinical measures of disability and neuro-rehabilitation programs often focus on lower limbs impairment in PwMS. The present findings underline the frequency and the severity of upper limb involvement in people with progressive MS, in this cohort only the 13.7% had normal upper limb function. Dexterity was often at least mildly impaired in absence of weakness or increased tone. Neurophysiological measures of motor function were associated with clinical variables at both upper and lower limb. MEPs absence to the lower limbs in patients with impaired ambulatory function limit their use for the neurophysiological monitoring of progression in PMS due to ceiling effect. MEPs to the upper limb, despite milder clinical involvement, are often delayed but still measurable in people with PMS, thus providing a more suitable outcome measure for the functional monitoring of pyramidal function in this disease course.

References

Bohannon R, et al (1987). "Interrater reliability of a modified Ashworth scale of muscle spasticity." Physical Therapy 67(2): 206.
Erasmus LP, et al. (2001). Measurement of ataxic symptoms with a graphic tablet: standard values in controls and validity in Multiple Sclerosis patients. J Neurosci Methods.
Feys P, et al. (2017). Multiple Sclerosis Outcome Assessments Consortium. The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis. Mult Scler.
Livingston SC, et al. (2010). The influence of gender, hand dominance, and upper extremity length on motor evoked potentials. J Clin Monit Comput.

Disclosure

M. Pisa, S. Gelibter, Fichera M, Giordano A, Houdayer E, Chieffo R, Comola M: has nothing to disclose
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