Transcranial Magnetic Stimulation: Central to Peripheral Latency Ratios As Upper and Lower Motor Neuron Markers in Amyotrophic Lateral Sclerosis

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Objectives
To improve TMS diagnostic accuracy for ALS subtypes by incorporating the peripheral component of the total motor conduction time. This will be accomplished by creating a ratio of the UMN to L MN conduction latencies, thus normalizing the relative dysfunction of upper compared with lower motor neurons.

Background
Transcranial magnetic stimulation (TMS) evokes compound motor potentials through non-invasive stimulation of the cortex. TMS can be used in conjunction with spinal stimulation to evaluate upper motor neuron (UMN) and lower motor neuron (LMN) pathways by measuring total motor conduction times and peripheral conduction latencies. Abnormally prolonged central motor conduction time (CMCT) has been reported in patients with ALS and may be useful in revealing subclinical UMN involvement; however, TMS does not distinguish ALS subsets (ALS, PLS, familial ALS and PMA) using CMCT alone.

Methods
TMS was performed using a Cadwell MES-10 cap stimulator at Cz recording from the abductor digiti minimi and anterior tibial muscles. Maximal motor evoked response amplitudes were obtained at 100% MES-10 output. Electrical spinal (peripheral) stimulation was performed at C7 and T1 using a Digitimer High-Voltage Stimulator. Multiple channels were recorded simultaneously to minimize patient discomfort. Filter settings were 10 Hz for high pass and 10 kHz for low pass filters. Latencies were marked at a sensitivity of 200 µV/division. CMCT was calculated by subtracting the minimal latency achieved by supramaximal spinal stimulation of each muscle from the minimal latency achieved by optimized cortical stimulation.

Subjects

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>Average Age (years)</th>
<th>Gender</th>
<th>Disease Onset to 1st Test (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS</td>
<td>30</td>
<td>41 ± 12</td>
<td>M/F</td>
<td>25.5 ± 3.9</td>
</tr>
<tr>
<td>PLS</td>
<td>5</td>
<td>43 ± 8</td>
<td>4.2</td>
<td>3.8 ± 4.2</td>
</tr>
<tr>
<td>PMA</td>
<td>7</td>
<td>47 ± 12</td>
<td>7.8</td>
<td>1.6 ± 0.53</td>
</tr>
<tr>
<td>PALS</td>
<td>3</td>
<td>50 ± 7</td>
<td>0.3</td>
<td>3.6 ± 4.1</td>
</tr>
<tr>
<td>Controls/Normal</td>
<td>23</td>
<td>45 ± 12</td>
<td>MA</td>
<td>38.0 ± 3.3</td>
</tr>
</tbody>
</table>

Central Motor Conduction Times (CMCT) to ADM and TA

Central Motor Conduction Time to Abductor Digit Minimi (ADM)  
Central Motor Conduction Time to Tibialis Anterior (TA)

Central to Peripheral Ratios for normal and ALS subtype subjects

Results
Forty-three patients (30 ALS, 7 PMA, 6 PLS, and 3 FALS based on clinical examination) were studied. Though patients had a varying number of visits, only data from the first visit was analyzed. Based on central/peripheral ratios of conduction times, PMA patients had significantly lower central latency relative to peripheral latency in both the arms (p<0.02) and legs (p<0.03) compared to the other three subtypes (ALS, PLS, FALS). The mean ratio for PMA patients was 4.2±0.05 in the arms and 7.3±0.12 in the legs, as opposed to ratios of 3.9 to 9.1 (arms) and 9.6 to 1.38 (legs) for all other ALS subtypes. PLS ratios were the highest of the ALS subtypes but not significantly different due to the low number of cases.

Future Directions
CMCT and central to peripheral MCT ratios may be investigated further as tools for diagnosing and monitoring ALS. Both absolute and ratio values should be followed across multiple visits to determine the relationship between disease duration and progression. Both sets of values could be plotted over time and any acceleration or deceleration of disease progression could first correlate with clinical findings, and then perhaps investigated as a function of varying onset symptoms or treatment methods.

In addition, CMCT results from TMS should be correlated to Motor Unit Number Estimates (MUNE) to differentiate central from peripheral changes. Questions include: Does central or peripheral deterioration (as measured by TMS and MUNE, respectively) occur more rapidly? Does either test predict better or worse prognoses, and which combination of test results produces the highest predictive value over time? Does either test correlate more strongly with baseline clinical state and/or clinical changes? Preliminary collaboration shows that sensitivity and specificity of TMS and MUNE combined in detecting clinical UMN signs are greater than either test alone, with roughly 70% specificity and 55% sensitivity (Mitsumoto, 2004). Comparable issues could be addressed in comparing TMS to MRI.

The current combination of TMS and electrical stimulation techniques may also be used to compare CMCT in the spinal cord versus the brain across ALS subtypes. Also, investigation of changes in right versus left and proximal versus distal limbs may be useful prognostically. Finally, it is clear that more data is needed for non-standard ALS subtypes (PLS, PMA, and FALS) in order to obtain more definitive results.