

CASE SERIES

Abnormal central motor conduction at the upper but not lower limbs correlates with severe cervical spondylosis: discussion of an unexpected observation

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INTRODUCTION: A novel pattern of transcranial magnetic stimulation (TMS) abnormalities in cervical spondylotic myelopathy (CSM) comprising abnormal central motor conduction time (CMCT) to the upper limbs and normal CMCT to the lower limbs was observed. CSM was more severe radiologically and tended to be more severe clinically when this pattern was encountered.

CASE PRESENTATION: To further characterize this observation, 414 consecutive TMS evaluations of cervical spondylosis were reviewed. Those cases in which (a) CMCT was abnormal at the upper and (b) normal at the lower limbs and (c) a cervical spine magnetic resonance imaging (MRI) was available (UL_{abnormal} group) were included for further analysis. Cases where CMCT was abnormal at the lower limbs only (LL_{abnormal}) were used for comparison. MRI-measured sagittal and parasagittal diameters of the spinal canal at all intervertebral levels and cervical spinal cord T₂ hyperintensities were compared between these groups. Four patients fulfilled all inclusion criteria in each group. In UL_{abnormal}, all patients had T₂ hyperintensities, compared to none in LL_{abnormal} ($P=0.004$). The C₆₋₇ right ($6\text{ mm} \pm 1.05$ vs $8.48\text{ mm} \pm 4.01$, $P=0.05$) and left ($6.58\text{ mm} \pm 1.39$ vs $9.17\text{ mm} \pm 5.03$, $P=0.06$) parasagittal spinal canal diameters tended to be smaller in UL_{abnormal}. The modified Japanese Orthopaedic Association scale tended to be lower in UL_{abnormal} (11.5 ± 2.65 vs 15.75 ± 0.96 , $P=0.13$).

DISCUSSION: CMCT abnormalities isolated to the upper limbs constitute a less frequent pattern of involvement, which may correlate with more severe CSM.

Spinal Cord Series and Cases (2017) 3, 17009; doi:10.1038/scsandc.2017.9; published online 16 March 2017

INTRODUCTION

Central motor conduction time (CMCT), measured by transcranial magnetic stimulation (TMS), is an estimate of the conduction time of corticospinal fibers between motor cortex and spinal (or bulbar) motor neurons. It includes the times for excitation of cortical cells, conduction via the corticospinal tract and excitation of the motor neuron sufficient to exceed its firing threshold. The estimate is made by subtracting the spinal motor neuron-to-muscle latency from the cortex-to-muscle latency.¹ CMCT is sensitive in detecting cervical spondylotic myelopathy (CSM), which is caused by compression of the cervical spinal cord by spondylotic changes, while it correlates with the severity of cord compression.¹⁻³ CMCT to lower limb muscles is more sensitive and is earlier affected, while upper limb CMCT is affected later in the course of CSM and indicates more severe disease.^{4,5}

It was observed in a minority of patients seen in our laboratory that CMCT to the upper limbs was abnormal, while that to the lower limbs was normal. This pattern of involvement correlated with more severe disease radiologically, with a trend toward more severe clinical symptoms. Here we discuss this unexpected finding.

MATERIALS AND METHODS

All TMS evaluations of cervical spondylosis conducted between October 2008 and July 2016 were retrospectively analysed. Those cases were included for further analysis where (a) CMCT was measured at all four limbs, (b) lower limb CMCT was normal, (c)

upper limb CMCT was abnormal and (d) a cervical spinal MRI was available to allow the study of spine anatomy in relation to TMS results. This last inclusion criterion was imposed by the fact that many patients had been referred for TMS evaluation alone; therefore, a spine MRI was not always available.

TMS evaluation comprised determination of CMCT at the upper and lower limbs bilaterally, according to the F-Wave method.⁶ Motor evoked potentials were recorded from the abductors digiti minimi at the upper limbs and from the extensors digitorum brevis or the tibialis anteriori at the lower limbs, using a circular coil (MC-125, MagVenture, Farum, Denmark) positioned over the vertex. CMCT at the abductors digiti minimi was considered abnormal if it was higher than 9.81 ms or the inter-side difference was higher than 2.78 ms. For the extensors digitorum brevis, an abnormal test was defined as CMCT >17.7 ms or inter-side difference >3.35 ms, and for the tibialis anteriori as CMCT >18.61 ms or inter-side difference >3.49 ms (laboratory-established normal values).

For spinal canal measurements, axial T₂ MRI sections were made at the intervertebral levels from C₂₋₃ to C₆₋₇. The slice planes were set parallel to each intervertebral disc space. Spinal canal diameters were measured at all levels with the aid of image-processing software.⁷ The midline anteroposterior diameter was measured at the midline as the distance between the posterior margin of the intervertebral disc and the anterior margin of the ligamentum flavum ($d_{\text{mri_midline}}$). Lateral anteroposterior diameters were also measured at 50% of the distance between the midline and the left ($d_{\text{mri_left}}$) and right ($d_{\text{mri_right}}$) border of the spinal canal (Figure 1). The lateral borders were set at the interior

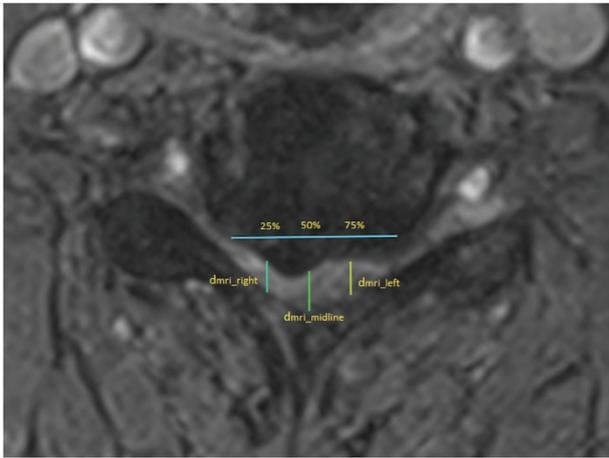


Figure 1. An axial T₂ MRI section of UL_{aboriginal} patient #4 at the C₅₋₆ level and the related spinal canal dimensions.

margins of the pedicles. MRI was further evaluated for spinal cord T₂ signal hyperintensities, while radicular lesions were screened by electromyogram.

Patients in whom (a) CMCT was measured at all four limbs, (b) lower limb CMCT was abnormal, (c) upper limb CMCT was normal and (d) a cervical spinal MRI was available were recruited for comparison. The same TMS and MRI parameters were measured in this second group and were compared between the two groups: patients with abnormal CMCT at the upper limbs (UL_{aboriginal}) or the lower limbs (LL_{aboriginal}). The aim was to identify anatomical characteristics in the cervical spine MRI that could account for the selective involvement of the upper or lower limb CMCT in TMS and to correlate said MRI characteristics with different pathophysiological mechanisms, if possible.

Patients with abnormal CMCT at both the upper and lower limbs were not included in the analysis. This pattern of involvement might have occurred as a result of (a) a long-standing lesion initially affecting the lower limbs, which by time progressed to the upper limbs, or of (b) a lesion that initially affected the upper limbs, as in the UL_{aboriginal} group, but progressed to the lower limbs by time, or of (c) a severe lesion, which affected all four limbs right from the beginning. As it would not be possible to differentiate between these cases on the basis of a single TMS and MRI evaluation for each patient, this group could have confounded our results.

Two-tailed Fisher's exact test was used for between-group comparisons. Rates were compared with the Barnard test.⁸ All calculations were done in LibreOffice 5.2.

RESULTS

Of the 414 consecutive TMS evaluations performed, isolated upper limb CMCT abnormalities were seen in 15 patients (3.7%), isolated lower limb abnormalities in 62 (15%), combined upper and lower limb abnormalities in 141 (34%), while the remaining 196 evaluations (47.3%) were normal. However, all inclusion criteria were fulfilled by four patients with isolated upper limb abnormalities (UL_{aboriginal} group) and four patients with isolated lower limb abnormalities (LL_{aboriginal} group). The demographic, clinical (expressed in terms of the modified Japanese Orthopaedic Association assessment scale (modified-JOA)⁹) and TMS evaluations of patients in the UL_{aboriginal} and LL_{aboriginal} groups are shown in Table 1. The MRI measurements are shown in Table 2.

Table 3 compares modified-JOA and MRI measurements between the two groups. Spinal canal diameters (d_{mri_right} , $d_{mri_midline}$ and d_{mri_left}) were not significantly different at C₂₋₃, C₃₋₄, C₄₋₅ and C₅₋₆. At C₆₋₇ d_{mri_right} and d_{mri_left} were smaller in UL_{aboriginal} with borderline statistical significance ($P=0.05$ and

Table 1. Demographic, clinical and TMS characteristics of patients with isolated upper (UL_{aboriginal} group) and lower (LL_{aboriginal} group) limb abnormalities

	Patient #1	Patient #2	Patient #3	Patient #4
<i>UL_{aboriginal} group</i>				
Sex	Male	Female	Female	Male
Age	80	72	44	72
Modified-JOA	8	14	13	11
CMCT (ms)				
Right upper limb	11.12	13.5	9.31	9.9
Left upper limb	8.62	13.23	4.5	4.12
Inter-side difference	2.48	0.27	4.81	5.78
Right lower limb	15.47	15.5	14.81	17.13
Left lower limb	15.5	16.25	12.5	17
Inter-side difference	0.03	0.75	2.31	0.13
Radicular lesions	No	No	No	C ₈ right/chronic
<i>LL_{aboriginal} group</i>				
Sex	Male	Female	Female	Male
Age	70	34	32	55
Modified-JOA	15	17	16	15
CMCT (ms)				
Right upper limb	6.6	4	7.5	8.26
Left upper limb	4.5	3.5	8.4	7.3
Inter-side difference	2.1	0.5	0.9	0.96
Right lower limb	11.6	14.29	15.7	18.3
Left lower limb	16.7	8.26	11.3	16
Inter-side difference	5.1	6.03	4.4	2.3

Abbreviations: CMCT, central motor conduction time; modified-JOA, modified Japanese Orthopaedic Association; TMS, transcranial magnetic stimulation.

$P=0.06$, respectively). $d_{mri_midline}$ was not significantly different. Furthermore, all patients in UL_{aboriginal} had T₂ hyperintensities, compared to none in LL_{aboriginal} ($P=0.004$).

The level of T₂ hyperintensities in the UL_{aboriginal} group did not always correspond to the level of maximum stenosis in MRI. In patient #1 (Table 2), maximum stenosis was seen at level C₆₋₇, while T₂ hyperintensity was evident at C₃₋₄. In patient #2, hyperintensity was evident at C₃₋₄, while maximum stenosis occurred at C₅₋₆ and C₆₋₇. In patient #3, hyperintensity was seen at C₅₋₆, while significant stenosis occurred at C₄₋₅, C₅₋₆ and C₆₋₇ (maximum at C₆₋₇). In patient #4, hyperintensity was found at C₃₋₄ and stenosis was observed at all C₃₋₄, C₄₋₅, C₅₋₆, C₆₋₇ levels (maximum at C₅₋₆).

There were no findings of radicular lesions in the electromyogram in any of the patients, with the exception of patient #4 in UL_{aboriginal}, where EMG yielded signs of chronic denervation and re-innervation at the level of C₈, on the right (a discrete maximum voluntary contraction diagram and high-amplitude motor unit were recorded from the abductors digiti minimi).

Modified-JOA was not significantly different between the two groups, although there was a trend toward higher values (better clinical condition) in LL_{aboriginal}.

DISCUSSION

It is commonly accepted that CMCT to lower limb muscles is more sensitive and is earlier affected, while upper limb CMCT is affected later. This belief is supported by many published studies.²⁻⁵ Under time pressure one might opt to study CMCT to the lower limbs only, assuming that if it is normal then CMCT to the upper limbs should be normal as well. Here initial evidence is provided against this belief. In a small, yet measurable, subset of patients, CSM manifested with isolated upper limb TMS abnormalities, leaving

Table 2. Cervical MRI measurements of patients with isolated upper (UL_{abnormal} group) and lower (LL_{abnormal} group) limb abnormalities: transverse diameter of the spinal canal at the midline (d_{mri_midline}) and at 50% of the distance between the midline and the left (d_{mri_left}) and right (d_{mri_right}) border of the spinal canal, at all intervertebral levels

	Patient #1	Patient #2	Patient #3	Patient #4
<i>UL_{abnormal} group</i>				
C ₂₋₃	9,57/10,8/11,5	11,7/12,4/10,6	9,25/9,75/10,1	9,18/9,23/7,66
C ₃₋₄	9,17/10,4/9,6	7,77/9,59/7,67	8,62/10,5/9,24	6,53/7,46/6,24
C ₄₋₅	9,19/9,59/9,25	8,62/9,37/7,45	5,87/8,19/6,34	5,73/7,27/6,18
C ₅₋₆	8,98/10/9,09	5,14/8,75/5,83	6,43/7,32/5,58	4,16/5,37/3,85
C ₆₋₇	7,45/10,4/8,23	6,11/8,74/6,84	5,18/8,14/6,38	5,27/6,83/4,86
T ₂ hyperintensity	C ₃₋₄	C ₃₋₄	C ₅₋₆	C ₃₋₄
<i>LL_{abnormal} group</i>				
C ₂₋₃	7,08/8,8/7,68	11,5/11,8/10,5	12,3/12,9/11,3	5,7/6,76/6,1
C ₃₋₄	7,7/3/4,56	9,26/10,7/8,63	8,98/11,5/10,4	5,45/5,64/7,06
C ₄₋₅	6,69/6,7/4,88	7,91/9,14/8,69	9,69/10,8/9,22	4/5,44/5,22
C ₅₋₆	6,89/8,9/7,65	7,11/10,8/9,11	5,74/9/7,11	5,38/5,8/5,45
C ₆₋₇	12,2/14/15,3	9,59/10,9/8,82	9,33/11,4/9,55	2,78/4,4/3,01
T ₂ hyperintensity	No	No	No	No

Measurements are shown in millimeters as d_{mri_right}/d_{mri_midline}/d_{mri_left}.

Table 3. Comparison of modified-JOA and cervical MRI diameters and T₂ hyperintensities, as described in Table 2, between patients with isolated upper (UL_{abnormal} group) and lower (LL_{abnormal} group) limb abnormalities

Parameter	UL _{abnormal}	LL _{abnormal}	Significance
<i>C₂₋₃</i>			
d _{mri_right}	9.93 ± 1.2	9.15 ± 3.25	NS
d _{mri_midline}	10.55 ± 1.4	10.07 ± 2.8	NS
d _{mri_left}	9.97 ± 1.64	8.9 ± 2.43	NS
<i>C₃₋₄</i>			
d _{mri_right}	8.02 ± 1.15	7.67 ± 1.79	NS
d _{mri_midline}	9.49 ± 1.41	8.79 ± 2.78	NS
d _{mri_left}	8.19 ± 1.55	7.66 ± 2.48	NS
<i>C₄₋₅</i>			
d _{mri_right}	7.35 ± 1.81	7.07 ± 2.39	NS
d _{mri_midline}	8.61 ± 1.08	8.02 ± 2.41	NS
d _{mri_left}	7.31 ± 1.41	7 ± 2.27	NS
<i>C₅₋₆</i>			
d _{mri_right}	6.18 ± 2.09	6.28 ± 0.85	NS
d _{mri_midline}	7.86 ± 1.99	8.63 ± 2.08	NS
d _{mri_left}	6.09 ± 2.99	7.33 ± 1.51	NS
<i>C₆₋₇</i>			
d _{mri_right}	6 ± 1.05	8.48 ± 4.01	0.05
d _{mri_midline}	8.53 ± 1.48	10.18 ± 4.08	NS
d _{mri_left}	6.58 ± 1.39	9.17 ± 5.03	0.06
T ₂ hyperintensities	4/4	0/4	0.004
Modified-JOA	11.5 ± 2.65	15.75 ± 0.96	0.13

Abbreviations: modified-JOA, modified Japanese Orthopaedic Association; NS, not significant. Measurements are shown as mean ± s.d.

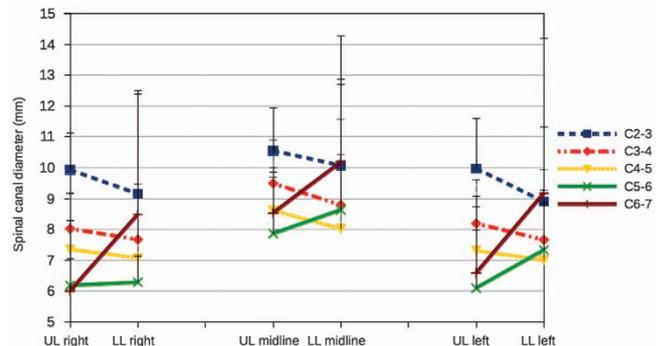


Figure 2. Comparison of mean spinal canal diameters and T₂ hyperintensities at all intervertebral levels for the UL_{abnormal} and LL_{abnormal} groups. At C₅₋₆ and C₆₋₇ mean diameters in UL_{abnormal} are smaller, especially UL_{abnormal} d_{mri_right} and d_{mri_left}, for which the differences are borderline significant. T₂ hyperintensities are significantly more frequent in UL_{abnormal}.

suspected CSM (414 patients) is among the biggest found in the literature; therefore, the small number of patients with isolated upper limb abnormalities may reflect the rarity of this condition. Four such patients were included in this study, while in another 11, the results of TMS evaluation were consistent with this pattern, but cervical MRI was not available. Thus, the frequency of isolated upper limb CMCT abnormalities in this series ranges from a validated lower limit of 1% (4/414) to a potential upper limit of 3.7% (15/414).

The number of patients with isolated lower limb CMCT abnormalities, who served as comparators, was also small (four patients); because CMCT to the lower limbs is affected first, as discussed above, more patients would have been expected to have presented with this pattern of TMS findings, compared to those with isolated upper limb abnormalities. Indeed, 62 patients (15%) in total fulfilled the TMS criteria, but MRI was not available in most of them. Thus, only four fulfilled all inclusion criteria for this study. The small number of patients fulfilling all inclusion criteria may have been responsible for the borderline significance found in MRI measurements and in clinical scores. Confirmation of these findings in larger studies is thus warranted.

The pathophysiological underpinnings of the different patterns of involvement of upper and lower limb pyramidal tracts in CSM are not entirely clear. Blood flow supply changes to the cervical

cord, leading to ischemia, demyelination and axon loss have all been implicated in the pathogenesis of CSM.^{4,9,10,11} It has been suggested that when there is a close correlation between MRI and TMS findings, the most important etiological factor may be probably a segmental demyelination of central motor pathways due to a direct mechanical spinal cord compression. When discrepancies between the level of spinal cord compression documented by neuroimaging studies and the level of spinal cord dysfunction revealed by TMS are observed,^{3,12} more mechanisms come into play. A more caudal functional involvement of the cervical cord revealed by TMS has been attributed to compromised blood flow to the spinal cord. The anterolateral regions of lower cervical segments are blood supplied almost exclusively from the anterior spinal artery, whereas the higher cervical segments that are located between the cervical and intracranial arterial territories have more sources of blood. Therefore, the frequent involvement of lower cervical segments may depend on their higher vulnerability to ischemic damage. When cervical spondylotic compression involves the anterior spinal artery, the major damage is of vascular origin and localized to lower cervical segments, independent from the level of spondylotic degenerative changes.^{3,13} These observations are mostly based on evidence stemming from small, older anatomical studies; hence, more work is needed to fully elucidate the pathophysiological mechanisms involved in CSM. Nevertheless, histological findings of both spinal cord ischemia and demyelination have been found in autopsy material in said studies,^{14,15} alluding to the fact that both these mechanisms come into play in CSM.

We hypothesize that ischemic damage is the major pathogenetic factor in patients presenting with isolated upper limb CMCT abnormalities. Older anatomical studies, from the work of Adamkiewicz in 1881¹⁶ up to that of Chakravorty in 1969,¹⁷ have suggested that the cervical radicular arteries, that is, the arteries accompanying the nerve roots entering through the intervertebral foramina, also supply the spinal cord. Dye injected into these arteries was capable of filling both anterior and posterior arteries in the cervical cord.¹⁷ These radicular arteries may originate from any branch of the subclavian artery in the neck, that is, from the vertebral, costocervical and thyrocervical trunks. In the upper six segments, they can arise from the vertebrae or from the ascending cervical branch of the thyrocervical trunk, and the spinal branches of these two vessels always anastomose.¹⁷

In most cases the cervical radicular arteries are two or three; in up to two-third of cases there is only one such artery.¹⁷ They accompany more frequently the C₄₋₆ nerve roots and very rarely C₃, C₇ and C₈.¹⁷ It has been suggested that if the radicular artery (or arteries) is occluded the risk of spinal cord ischemia increases. The risk is greater if there is only a single major radicular artery, which is occluded and is more likely to occur at the presence of lateral disc protrusion, when the protruding disc is in closer anatomical relation to said artery.¹⁷

Indeed, in our UL_{abnormal} patients, the lateral diameters of the spinal canal (d_{mri_right} and d_{mri_left}) at C₆₋₇ were smaller compared to LL_{abnormal}, albeit with borderline statistical significance, while there was a trend for lower diameters at C₅₋₆, where most radicular arteries are found. Figure 1 shows an axial T₂ MRI section of UL_{abnormal} patient #4 at the C₅₋₆ level. Significant right lateral stenosis is obvious, while CMCT is also prolonged at the right upper limb. The role of ischemia in this pattern of TMS abnormalities is further supported by the fact that in three of the four UL_{abnormal} patients, T₂ hyperintensities were seen rostral (C₃₋₄) to the level of stenosis (C₄₋₅, C₅₋₆ and/or C₆₋₇). In the remaining patient, stenosis extended from C₃₋₄ to C₆₋₇. LL_{abnormal} patients, in whom T₂ hyperintensities were not seen in the MRI,

also had considerable stenosis, but less than that in UL_{abnormal} patients at C₅₋₆ and C₆₋₇. The mean spinal canal diameters at all intervertebral levels for the two groups are shown side-by-side for comparison in Figure 2. At C₅₋₆ and C₆₋₇ mean diameters in UL_{abnormal} are smaller compared to LL_{abnormal}, with borderline statistical significance.

In conclusion, we have observed that in a small subset of patients with CSM, TMS discloses isolated upper limb CMCT abnormalities. This pattern of involvement correlates with more severe disease, both clinically and radiologically, and should be sought by neurophysiologists, who should not limit their evaluation to the, commonly accepted as more sensitive to CSM, lower limbs. As this was a relatively rare finding in the present series, confirmation by other researchers is warranted, while more detailed studies are needed to elucidate its pathophysiological underpinnings.

COMPETING INTERESTS

The author declares no conflict of interest.

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