The assessment of neuronal dysfunction in motor neuron disease using proton magnetic resonance spectroscopy: Correlation with clinical findings.

CM Ellis, A Simmons, I Newsom-Davis, C Andrews, A Glover, M Adamson, SCR Williams, PN Leigh. Department of Clinical Neurosciences, Institute of Psychiatry and Kings Healthcare, and Neuroimaging Dept, Maudsley Hospital, UK.

AIMS:
To evaluate neuronal dysfunction in the motor cortex and frontal region in motor neuron disease (MND) using volume localised proton magnetic resonance spectroscopy ('H-MRS) and to correlate clinical and neuropsychological features with peak area metabolite ratios.

INTRODUCTION:
A number of studies have demonstrated a reduction in NAA in the motor cortex in motor neuron disease\(^1,^2,^3\), but the role of 'H-MRS as an aid to the diagnosis of the disease and in monitoring its progression remains unclear. Likewise, information on the correlation of clinical features with the measured metabolites is sparse\(^4\).

It is well recognised that the pathological processes in MND extend beyond the motor cortex. PET activation paradigms have been combined with neuropsychological assessment to demonstrate abnormalities of frontal lobe function in non demented ALS patients\(^1,^2,^5\). However, it remains unclear whether cognitive dysfunction defines a separate subgroup in ALS, and whether the abnormalities demonstrated by PET studies and neuropsychology in non demented ALS patients are due to neuronal loss in the frontal regions.

SUBJECTS AND METHODS
Clinical base:
Sixteen patients with El Escorial definite, probable or possible MND were studied, 8 with limb onset (mean age 55.5±15.2 yrs) and 8 with bulbar onset (m=8, mean age 54.3±14.2 yrs), and compared with 8 healthy, age matched controls (mean age 55.8±14.9 yrs). The control subjects were non related friends or spouses of the patients.

Clinical Assessments:
All patients underwent physical examination. Disease severity was estimated using the ALS severity scale, evaluating bulbar and spinal function as well as overall disease severity. Muscle strength was assessed by the same examiner using the MRC rating scale. The modified Ashworth spasticity scale and a reflex scale, an unvalidated scale devised in our institute, were used to assess upper motor neuron involvement. A battery of standardised, routinely used neuropsychological procedures was delivered, together with additional more experimental measures, to address specific deficits in ALS.

Magnetic Resonance Spectroscopy:
Single voxel 'H-MRS was performed using a 1.5 Tesla GE Signa MR system (General Electric, Milwaukee, WI). The brain was initially imaged in 2 orthogonal planes, sagittal (fast spoiled grass, TR=150ms, TE 4.2ms, 6=90°, field of view=22cm) and axial (proton density weighted fast spin echo, TR=4000ms, TE=17ms, echo train length=8), to identify the 3 volumes of interest (VOIs): motor, frontal and parieto-occipital, with the voxel centred as much as possible on subcortical white matter. Spectra were obtained with a PRESS localisation sequence for each VOI, initially using an echo time of 136ms, repetition time 2000ms, 2000 data points and a bandwidth of 2500Hz. Water suppression was carried out by a sequence of chemical shift selective (CHESS) RF pulses. The first spectrum was followed by a repeat sequence at an echo time of 272ms without repositioning the VOI or changing the shims or water suppression flip angle.

The areas of the major resonances (NAA, (Cr+PCr) and Cho) at 2.02, 3.03 and 3.22ppm were determined by Levenberg-Marquart fitting to Lorentzian line shapes using software provided by the manufacturer (SAGE/IDL, GE Medical Systems, Milwaukee, WI).

From these, three peak area ratios were determined: NAA/(Cr+PCr), NAA/Cho and Cho/(Cr+PCr). The analysis protocol is independent of the observer.

RESULTS
Motor region:
On comparison of the total ALS group and normal controls, no significant differences were found between the metabolite peak area ratios in the motor region at either echo time (136 or 272 ms).

However, significant correlations were found in the motor cortex (TE 136ms) in MND patients between the El Escorial category and NAA/(Cr+PCr) ratio. Significant correlations were also found between the total score on the ALS severity scale and measured ratios of NAA/(Cr+PCr) (r=0.631, p=0.014) and Cho/(Cr+PCr) (r=0.567, p=0.027) in the motor cortex. Muscle strength was correlated with NAA/(Cr+PCr) ratio and just failed to reach statistical significance (r=0.43, p=0.08). Reflex score, Ashworth spasticity scale and disease duration showed no significant correlation with the NAA/(Cr+PCr) ratio (p>0.16).

Bulbar onset patients were found to have a significantly lower NAA/(Cr+PCr) ratio in the motor region at TE 136ms compared with limb onset patients (p=0.03).

Frontal region:
No significant differences were found in any of the metabolite peak area ratios between the three subject groups at TE 136ms. At TE 272ms, the Cho/(Cr+PCr) ratio was reduced in the complete ALS group compared to controls (p=0.01).

The NAA/Cho ratio showed a strong negative correlation with the Stroop quotient (r=0.665, p=0.002) and was positively correlated with the Picture Arrangement average (r=0.478, p=0.026).

Occipito-parietal region:
No significant differences were found in any of the metabolite peak area ratios between the three subject groups at TE 136ms. At TE 272ms, the Cho/(Cr+PCr) ratio was reduced in the limb onset compared with the bulbar onset group (p=0.05).

DISCUSSION:
We have been able to demonstrate evidence of neuronal loss or dysfunction in the motor region in ALS, particularly in the bulbar onset group, using single voxel proton magnetic resonance spectroscopy, but the considerable overlap between metabolite peak area ratios in patients and controls precludes its use as a "front-line" diagnostic tool. We have been unable to demonstrate differences in frontal lobe metabolite ratios depending on the mode of onset of ALS, and it seems more likely that frontal lobe dysfunction is related to bulbar symptomatology, independent of the mode of onset. As spectral acquisition times decrease and multi-voxel spectroscopy improves, the sensitivity of MRS may afford more comprehensive investigation of neuronal loss and/or dysfunction in ALS.

REFERENCES:
1 Pliero EP et al Neurology 1994 44 1933-1938
2 Jones AP et al J Neurol Sci 1995 128(suppl) 85-89
3 Oredal O et al 1997 Neurology 48 878-881
5 Abrahams S et al Brain 1996 119 2105-2120
6 Kew JJ et al Brain 1993 1399-1423