Vascular versus neuronal defects in Amyotrophic Lateral Sclerosis: an fMRI study.

C. Sage[1], R. Peeters[1], W. Robberecht[2], S. Sunaert[1]

[1]Radiology, University Hospital of the Catholic University of Leuven, Leuven, Belgium, [2]Neurology, University Hospital of the Catholic University of Leuven, Leuven, Belgium

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative condition of complex pathology in humans, primarily involving motor neurons in the cerebral cortex (upper motor neurons, UMN), the brainstem and the spinal cord (lower motor neurons, LMN). It results in progressive weakness and wasting of the bulbar, limb, thoracic and abdominal musculature due to a loss of innervation of these muscles. Patients will lose the ability to generate and execute voluntary movements. Histopathologically, the loss of cells of Betz in the primary motor cortex is the predominant observation, but the aetiology of this disease remains poorly understood. Apart from neuronal loss, vascular deficits could play a role in the in vivo physiopathology of ALS. In molecular studies, a direct effect of VEGF (vascular endothelial growth factor) on the survival of motorneurons has been demonstrated (1). Moreover, a low baseline expression of VEGF in humans has been established as a risk factor in the development of ALS. The action mechanism of VEGF in motorneuron survival might be either by a direct neuroprotective effect on the motorneurons or either by an indirect effect of VEGF on the vascular endothelial cells surrounding motorneurons (2). We performed an fMRI study, assessing the activation pattern in the brain while performing a motor task, an imaginary motor task and an alternating hyperventilation/breath-hold task. The latter is performed to assess the vascular reactivity in the brain without interference of task-induced activations and visualizes the capacity of the cerebral vasculature to stress conditions. The obtained activation patterns were compared to sex- and age-matched controls, to evaluate whether the motor impairment seen in ALS patients can be attributed to vascular and/or neuronal defects in the brain using BOLD fMRI.

Methods and materials

Thirty-three ALS patients and 21 controls underwent fMRI examination on a 3T scanner (Intera, Philips, Best, the Netherlands) with a 8 channel phased array head coil. In the first session, subjects performed a motor task with the right hand in either a movement or an imagery mode of performance. The experiment was performed in a classical block-design with three different blocks (two action blocks of movement and imagery and a fixation/resting block) lasting 30 seconds each that were repeated three times in the session. The primary interest of this task was to assess the differences and similarities between patients and controls in both motor conditions versus rest. In the second session, an alternating hyperventilation/breath-hold task was performed, consisting of 20 seconds of breath-holding following 20 seconds of hyperventilation, during 6 minutes of scanning. Visually presented stimuli of the expected task to be performed guided both sessions throughout.

The two sessions of fMRI were imaged using single shot EPI (120 dynamic scans; 34 axial slices; FOV= 230x230 mm; matrix= 112x112 mm; slice thickness= 4 mm; TR= 3000 ms; TE= 33 ms; TA= 6,07 minutes) and a T1-weighted coronal 3D TFE (182 contiguous coronal slices; FOV= 250x250 mm; TE= 4,6ms; TR= 9,7 ms; slice thickness= 1,2 mm; matrix= 256x256 mm; voxel size= 0,98x0,98x1,2 mm; TA = 6,3 minutes) was also acquired.

Image analysis was performed using statistical parametric mapping (SPM2, Wellcome Department of Imaging Neuroscience, University College London). Functional data were realigned and motion corrected using the preprocessing procedures of SPM. Analyses were done on images which were spatially normalized to match the MNI template and smoothed with a Gaussian kernel of 6 mm full width at half maximum. Contrasts were generated for movement vs rest and imagery vs rest for the first session, and breath-hold vs hyperventilation for the second session. Threshold for these contrast was set at p=0,05 corrected for multiple comparisons. Group comparisons between patients and controls for these effects were performed using random effects analysis and contrasts were thresholded at p=0,001.

Results

In the fMRI motor task both groups showed activation of areas typical for voluntary movement, notably contralateral primary sensorimotor cortex, premotor cortex, supplementary motor cortex, posterior parietal, basal ganglia, and ipsilateral cerebellum (see Fig. 1). In ALS patients, there was a recruitment of both motor and extramotor areas, mostly ipsilaterally. The ROI analysis showed significant increase of %MR signal change of motor areas (except M1) in ALS patients. In the imaginary task, a similar significant recruitment of ipsilateral motor areas was observed (also Fig.1).

Vascular reactivity (Fig. 2) seemed to be impaired in ALS patients mostly in the primary motor cortex and to a lesser degree in other frontal cortical areas, whereas there was no difference in vascular reactivity in the visual cortex.

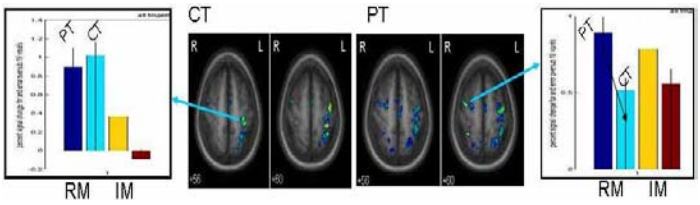

Fig.1 : first fMRI session. Representative fMRI activation maps of ALS patients (PT) and controls (CT), with MR% signal change graphs (contralateral primary motor cortex on the left; ipsilateral premotor cortex on the right) during real movements (RM) and imaginary motor tasks (IM).

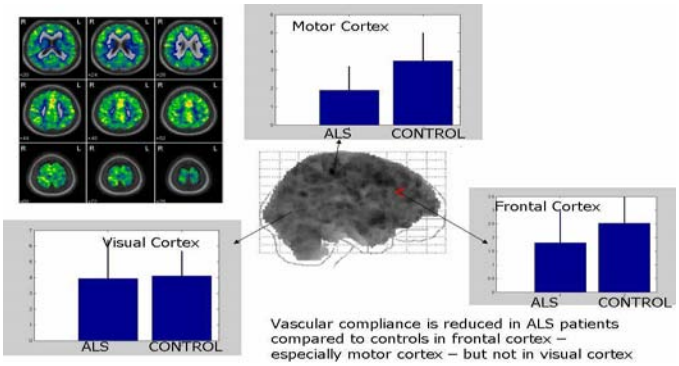

Fig.2 : second fMRI session. Representative vascular reactivity maps of ALS patients and controls, with MR% signal change graphs (Breath-hold versus hyperventilation). Note decreased vascular reactivity in motor cortex and frontal lobe.

Conclusion

ALS patients recruit additional areas for the generation of voluntary movement when compared to healthy controls.

vascular compliance is reduced in frontal regions and especially primary motor cortex of ALS patients when compared to healthy age- and sex-matched controls. Thus, this suggests that there are both vascular and neuronal defects, possibly mediated through a decreased VEGF expression, leading to the physiopathology seen in ALS.

References

(1) Van Den Bosch et al. 2004 Neurobiology of disease 17; 21-28.

(2) Lambrechts et al. 2004 Nature genetics 34(4); 383-394