Are there vascular deficiencies in amyotrophic lateral sclerosis?

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Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease predominantly affecting the motor system. Accumulating evidence is now pointing to a more widespread involvement of cortical areas, with ALS being termed a multisystem disease nowadays (1). However it has always been considered a strictly neurodegenerative disease, studies performed in other neurodegenerative diseases such as Alzheimer's disease (2) and other imaging studies in ALS (3) might suggest a vascular component in the in vivo physiopathology of ALS.

In order to assess this possible vascular contribution to ALS, we performed an fMRI study, in which the activation pattern in the brain induced by an alternating hyperventilation/breath-hold task was assessed. This task allows the evaluation of the cerebrovascular reactivity (CVR) of the brain, which reflects the intrinsic ability of the cerebral circulation to adapt the vasomotor tone to vasodilatory or vasoconstrictory stress. The obtained activation patterns were compared to those of controls, to evaluate whether vascular deficiencies may be present in ALS.

Methods and materials

Twenty-three ALS patients and 21 healthy age- and sex-matched controls were scanned using a 3T system (Intera, Philips, Best, the Netherlands) equipped with an eight channel phased-array head coil. A T1-weighted coronal 3D-TFE (182 contiguous coronal slices covering the whole brain and brainstem; FOV = 250 mm; TE = 4.6 ms; TR = 9.7 ms; slice thickness = 1.2 mm; matrix size = 256x256; voxel size = 0.98x0.98x1.2 mm; scan duration = 6:21 minutes) was acquired for image coregistration and overlay of functional MRI results. Functional MRI was performed using a gradient echo echo-planar imaging (GE-EPI) sequence (120 dynamic scans; 34 axial slices; FOV = 230 mm; TE = 33 ms; TR = 3000 ms; slice thickness = 4 mm; slice gap = 0.4 mm; voxel size = 1.8x1.8x4.0 mm; total scan time = 6:20 minutes).

The paradigm consisted of blocks of 21s of voluntary hyperventilation according to a prescribed pace of breathing, alternated with blocks of 21s of voluntary breath-holding. One fMRI session with a total scan time of 6 minutes thus comprised of 9 blocks of hyperventilation and 8 blocks of breath-holding. The instructions were projected onto a screen in front of the subject in the magnet bore.

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 pre-processing 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. First-level analysis consisted of generating contrasts for breath-hold versus hyperventilation, by using the individual global intensity changes for modelling the task. Threshold for this contrast was set at $p = 0.05$ corrected for multiple comparisons (FWE). The extent of activation was determined on individual contrast maps by counting the number of voxels that survived the statistical threshold of $p < 0.05$ FWE corrected. The total number of brain voxels of each individual was also determined, thus allowing the calculation of an activation index, which was determined as the ratio of the number of activated voxels over the total number of brain voxels. Possible differences in these quantities between patients and controls were evaluated by means of performing Student's t-test. Furthermore, a second-level analysis was performed to assess possible regional differences in CVR between the two groups. These group comparisons were performed using random effects analysis and contrasts were thresholded at p=0.001.

Results

The number of activation ratio of ALS patients was significantly lower than the activation ratio of controls (mean +/- standard deviation; PA: 0.45 +/- 0.16; CT: 0.65 +/- 0.12; $p = 0.000053$). This difference was not due to a lower number of brain voxels in ALS patients compared to controls (PA: 217891 +/- 8766; CT: 215035 +/- 9554; $p = 0.306935$), but to a significantly lower number of activated voxels in ALS patients) compared to controls (PA: 98341 +/- 34522; CT: 139922 +/-25641; $p = 0.000018$) (Fig. 1). The second level analysis showed that CVR was regionally decreased in ALS patients in the peripheral gray matter (Fig. 2), with the impairment being largely limited to the motor areas (primary motor area, premotor area, supplementary motor area) and frontal areas.

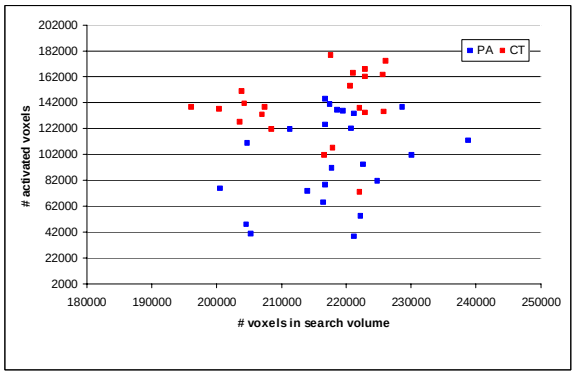

Fig. 1 : Scatterplot of number of brain voxels (x-axis) versus number of activated voxels (y-axis) in ALS patients (PA, blue squares) and controls (CT, red squares).

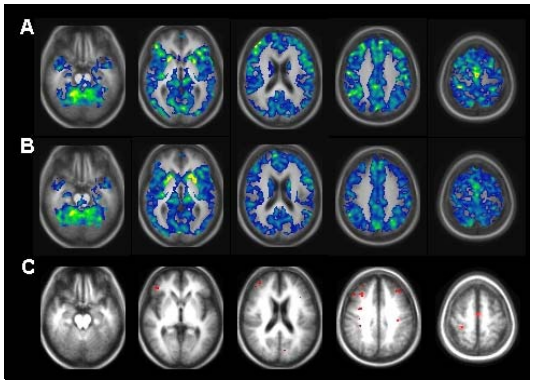

Fig. 2 :Mean cerebrovascular reactivity maps of controls (A) and ALS patients (B) and a contrast map showing regionally decreased CVR in ALS patients compared to controls (C).

Conclusion

CVR is reduced in frontal regions and especially motor areas of ALS patients when compared to healthy age- and sex-matched controls. This observation supports the idea of a vascular deficiency in ALS. Whether this deficiency represents a primary causal mechanism or secondary phenomenon in the in vivo physiopathology of ALS remains to be elucidated.

References

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