Cerebral Atrophy in End-Stage Renal Disease

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Introduction: End-Stage Renal Disease (ESRD) is reported to be associated with brain damage, usually seen as cognitive deficits or dementia, and generalized brain atrophy. Their precise etiology and mechanisms are unknown. Clinical research in this area is complicated by several factors, including comorbidities, which could cause brain damage and cognitive deficits by themselves, and the progressive nature of the disease, necessitating severity control. Previous reports of atrophy were non-quantitative. Here we report the first quantitative analysis of atrophy in these patients.

Methods: Ten ESRD patients being treated by hemodialysis (all male, age 61±10) were compared to 6 normal controls (4/6 male, age 78±7). Cognitive deficits were quantified with the Mini-Mental Status (MMS, Folstein et al., 1975). All subjects had 3D-MP-RAGE scans (axial slab of 160 slices, 1/.5 mm, yielding voxel dimensions .9x.9x1 mm, A>P PE (6/8 partial Fourier) with 25% phase oversampling and 30% slice oversampling, TR/TE/TI 2150/4.38/1100, FA 8, imaging time 8:38 min) on a 1.5T scanner (Siemens Symphony with Quantum gradients). Five patients had these scans after dialysis and five before dialysis; there were no significant differences between the pre and post conditions on any MP-RAGE variable. MRI data were quantified by our own Matlab routines, and the resulting images analyzed by SPM99 (http://www.fil.ion.ucl.ac.uk/spm/), using the optimized Voxel-Based Morphometry method (Good et al., 2001), 12mm smoothing and moderate correction, with a grey-matter template.

Results: Compartmental sizes were computed from SPM segmentation procedures. The patients had fewer grey matter (GM) voxels, fewer white matter (WM) voxels, and more CSF voxels, but none of the differences reached significance. Within the patients, age was correlated to the number of WM voxels (r= -.85, p<. 002); nonsignificant correlations also suggested loss of GM and increase of CSF with age. Within the controls, age was significantly correlated with GM volume (r= -.85, p<.05); the other correlations (NS) were also in the expected direction. Because the patients were significantly younger than the controls, these data suggest atrophy of the brain in ESRD patients: at equivalent ages the patients would have appreciably lower volume of GM.

The regional VBM analyses were, therefore, conducted as an ANCOVA with diagnosis (ESRD Vs Normal) as between-subject grouping factor and age as a covariate; all analyses were done at p=.001, uncorrected. We first examined the CSF compartment. ESRD patients had higher CSF amounts in multiple regions, mainly in cortical sulci and edges of the third and lateral ventricles. Significant differences were also found in the posterior aspect of the fourth ventricle, just above the pons, suggesting marked atrophy of the midbrain at the level of the colliculi (Fig. C.2.a). No cerebellar atrophy was noted. Normals did not show higher CSF anywhere.

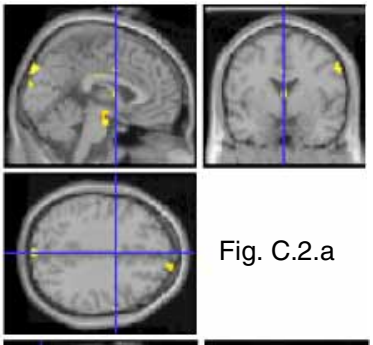

Fig. C.2.a

Significant positive correlations with age were found in numerous regions, mainly in frontal and parietal cortical surfaces and the third ventricle (Fig. C.2.b); the fourth ventricle was not related to age. There were no negative correlations with age. A similar VBM analysis was conducted for grey matter volume. Controls had higher GM volume bilaterally in the caudate nucleus (Fig C.2.c), and age was negatively correlated with GM volumes around the third ventricle. In no area were the HD patients higher than controls. No significant effects were found for WM. Seven ESRD patients had MMS values: MMS was correlated with the volume of CSF (r=-.89, p<. 05), the ratio of GM/CSF voxels (r=. 94, p<. 05), and the ratio of WM/CSF voxels (r=. 97, p<. 05). Greater cognitive deficits, thus, are associated with greater brain atrophy.

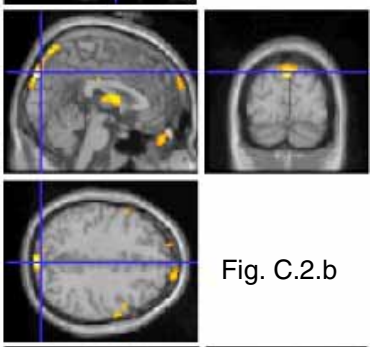

Fig. C.2.b

Discussion: Significant atrophy was found in ESRD patients, consisting of sulcal dilatation and (3rd & 4th) ventricular enlargement, after accounting for age effects. There was also loss of tissue focally evident in suprapontine areas of the midbrain and in the caudate nucleus. The brain stem finding is adjacent to, but different from, the pontine changes seen in Osmotic Demyelination Syndrome (Tarhan et al., 2004); none of our patients showed clinical symptoms consistent with that syndrome. The atrophy was related to both age and cognitive deficits in the expected directions. The focal effects in caudate and brain stem are novel and suggest directions for future research

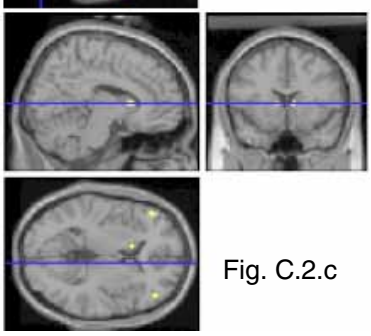

Fig. C.2.c

References:

Folstein et al., J Psychiatr Res 1975;12:189-198.
Good et al., NeuroImage 2001;14:21-36.
Tarhan et al., AJR 2004;182:809-816.