

Cerebral White Matter Disruption in Creutzfeldt-Jakob Disease

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Introduction: Creutzfeldt-Jakob Disease (CJD) is the most notable form of human prion diseases, characterized on MRI by focal diffusion reductions in the striatum, thalamus and cortex. Only one small study (3 patients)¹ has ever employed DTI (Diffusion-Tensor Imaging) in CJD. While pathological studies strongly suggest involvement of white matter pathways², which connect the known grey matter sites of degeneration, in vivo evidence has not been obtained. The current study provides robust evidence of change of white matter integrity in patients with a genetic form of CJD.

Methods: As part of a large prospective imaging study of CJD, 21 patients (13M/8F; age 59 ± 7 years) and 19 healthy controls (9M/10F; age 57 ± 10 years) were recruited. All patients were positive for the E200K mutation of the PRNP gene. Scanning was performed on a 1.5T GE system with a standard quadrature head coil. MRI sequences included a single-shot EPI DTI sequence with 25 contiguous axial-oblique slices, field of view (FOV) of 260 mm, repetition time (TR) of 8300 ms, echo time (TE) of 94 ms, and 5.0 mm slice thickness with reconstructed in-plane image resolution of 1.0x1.0 mm. The DTI sequence acquired a non-diffusion-weighted image ($b=0$ s/mm², T2-weighted) and a diffusion-weighted image ($b=1000$ s/mm²) along 25 gradient directions. The entire image processing pipeline for DTI was performed by FDT and TBSS tools provided by the FMRIB software package³. Common DTI indices were derived and voxel-wise image analysis of the FA was carried out using tract based spatial statistics (TBSS) with the default parameter setting. Group comparisons in normalized FA maps were tested by the non-parametric randomization method with age entered as a covariate. Significance was determined with the TFCE algorithm at $p < 0.05$, corrected for multiple comparisons. We also computed mean diffusivity (MD), axial (AD) and radial (RD) diffusivity.

Results: Figure 1 shows decreased FA among the patients compared to the controls in brainstem, cerebral peduncle, corticospinal tract, thalamus, internal capsule, external capsule, fornix, corpus callosum, and frontal lobe, corona radiata, posterior thalamic radiation, and sagittal striatum. No voxels survived in the direction of FA greater in patients than controls. Within those clusters, average FA was reduced in patients by 12 % compared to controls, AD was nearly equal between the groups (2%) while RD was substantially elevated (11%) among the patients. The mean FA of the significant voxels was significantly correlated with duration of illness ($r = -0.51$, $p < .05$) as shown in Figure 2.

Discussion: Grey matter diffusion reductions are well described in CJD⁴, and primarily involve the cerebellum, striatum, thalamus and cortex. All these brain areas are richly interconnected by known white matter pathways, and constitute known functional circuits concerned primarily with movement control. Although it is not clear exactly how white matter is affected by prions, animal models demonstrate deposition of PrP^{Sc}, astrocytes, and vacuolization, all of which are hallmarks of CJD pathology⁵. Our results document a progressive white matter abnormality in relevant pathways, that increases with disease duration. It is not yet clear whether the white matter abnormality follows, precedes, or coincides with the grey matter diffusion reductions. However, the distinct elevation of radial diffusivity strongly suggests disrupted myelin function or structure, and thus impaired conduction, which may explain some of the symptomatology as a disconnection syndrome.

References: 1 Fujita, K. et al. J Neurol Neurosurg Psychiatry 79, 1304-6 (2008). 2 Liberski, P. P. et al. Acta Neuropathol 97, 329-34 (1999). 3 Smith, S. M. et al. Neuroimage 31, 1487-505 (2006). 4 Lee, H. et al. Brain 132, 2680-2687 (2009). 5 Prusiner, S. B. Prions. Proc Natl Acad Sci U S A 95, 13363-83 (1998).

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