Cytoarchitecture of frontal cerebral cortex in variant Creutzfeldt-Jakob disease: Post mortem MR microscopy at 9.4 Tesla

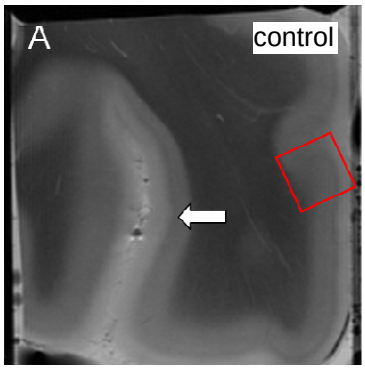
H. Hyare[1,2], P-W. So[3], J. S. Thornton[2], C. Powell[1,4], H. Parkes[5], D. Siddique[1], S. Wroe[1], S. Brandner[1,4], and T. Yousry[2]

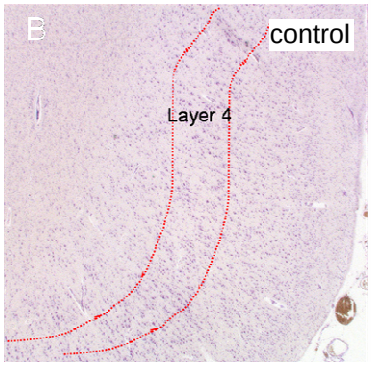
[1]MRC Prion Unit, Institute of Neurology, London, United Kingdom, [2]Lysholm Department of Neuroradiology, Institute of Neurology, London, United Kingdom, [3]Biological Imaging Centre, Imaging Sciences Department, MRC Clinical Sciences Centre, Hammersmith Hospital, Imperial College London, London, United Kingdom, [4]Division of Neuropathology, Institute of Neurology, London, United Kingdom, [5]Department of Neuroinflammation, Institute of Neurology, London, United Kingdom

Introduction: In the past decade there has been a growing interest in variant Creutzfeldt-Jakob disease (vCJD), known to be caused by the same prion strain as that causing Bovine Spongiform Encephalopathy (BSE)[1]. There are over 140 cases of vCJD in the UK alone and although a major epidemic has not occurred, the disease remains an important public health issue. For diagnosis, histopathologists often examine only the frontal cortex where the hallmarks of vCJD: spongiosis, gliosis and prion protein deposition[4] are evident. However, cortical changes on MRI in vCJD have not been extensively characterised, although bilateral thalamic high signal in the pulvinar nuclei on T2W and FLAIR images are reported with sensitivities of 78-100%[2,3]. Magnetic resonance microscopy (MRM) at 9.4T can resolve the horizontal lamination of the isocortex[5]. The purpose of this study was exploit this technology to characterise the laminar pattern of the frontal cortex in excised formalin-fixed specimens from patients who died from vCJD and a non-CJD control group, and to compare the results with histological findings.

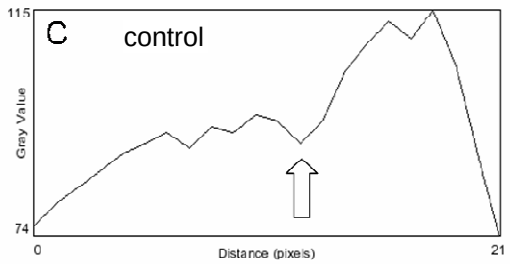
Methods: Formalin-fixed specimens from the frontal cerebral cortex from 6 patients who had died from vCJD (4 male, 2 female, mean age 41.6, range 19-76 years) and 6 non-CJD control subjects (1 male, 5 female, mean age 68.6, range 47 – 86 years) were imaged at 9.4T (Varian Inc, Palo Alto, CA). High resolution (78 micron in-plane) T2-weighted images were acquired (TE 24ms, TR 2400ms, FOV 40mm x 40mm, matrix 512 x 512, slice thickness 1mm, 20 averages) with a total acquisition time of 7 hours. Following MR imaging, 1 vCJD and 1 control specimen were selected and the fixed tissue incubated in 98% formic acid for 1 h and following further washing for 24 h in 10% buffered formal saline, tissue samples were processed, paraffin wax-embedded and stained with Nissl stain for microscopic evaluation. T2-weighted signal intensity profiles were generated perpendicular to the cortical surface, from deep to superficial areas, to more clearly depict the differences between vCJD and control specimens.

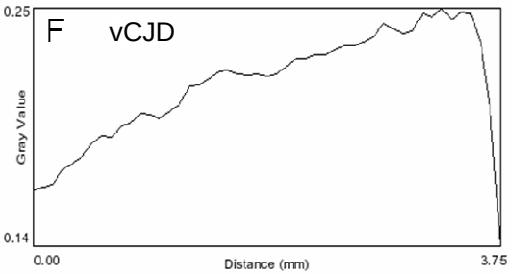
Results: Visual inspection of high resolution T2-weighted images of the frontal cortex revealed, in all 6 control specimens, an intracortical laminar structure with a low signal intensity layer (arrow, Fig A) corresponding to layer IV of the cortex (Fig B). However, in 5/6 vCJD specimens, there was apparent loss of the intracortical laminations with homogenous signal intensity across the cortex (see Fig D). In the remaining vCJD specimen the intracortical structure was attenuated but not completely absent. The cortical signal intensity profiles revealed a focal dip in intensity corresponding to layer IV in all 6 control specimens (Fig C) while for 5/6 vCJD cases the cortical signal intensities exhibited a smoother profile (Fig F). The Nissl staining performed in 2 of the specimens revealed attenuation of the intracortical structure in vCJD due to neuronal loss where there was spongiosis and prion protein deposition (Fig E).

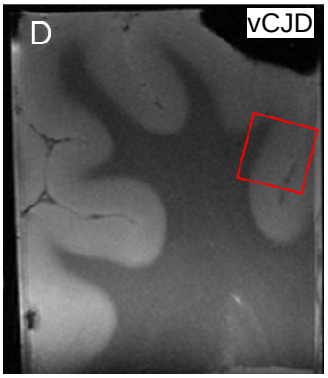


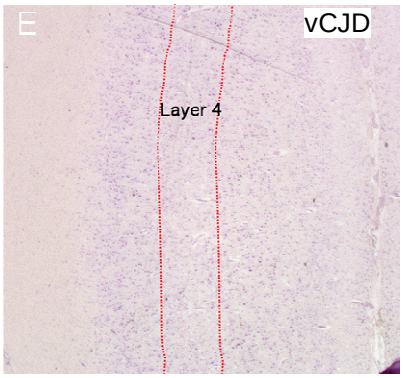


T2W MRI Histology Nissl Stain









T2W MRI Histology Nissl Stain

References:

(1) Malluci G. *et al* Curr Opin Neurol **17** 641-647 (2004)
(2) Zeidler M. *et al* Lancet **355** 1412-18 (2000)
(3) Collie D.A. *et al* AJNR **24** 1560-1569 (2003)
(4) DeArmond S. *et al* Prion Diseases.273-323 (2002)
(5) Fatterpekar G.M. *et al* AJNR **23** 1313-1321 (2003)

Conclusions: *Ex vivo* MRM at 9.4T can depict pathology characteristic of vCJD by demonstrating apparent loss of the normal intracortical laminations. These observations will be increasingly relevant as high-field MRI systems with improved spatial resolution enter clinical practice, when *in vivo* assessment of the cerebral cortex may prove highly beneficial in the diagnosis and monitoring of vCJD.