The Pulvinar Sign in variant Creutzfeldt-Jakob disease: quantitative diffusion-weighted imaging in vivo at 1.5T and ex vivo at 9.4T with histopathological correlation

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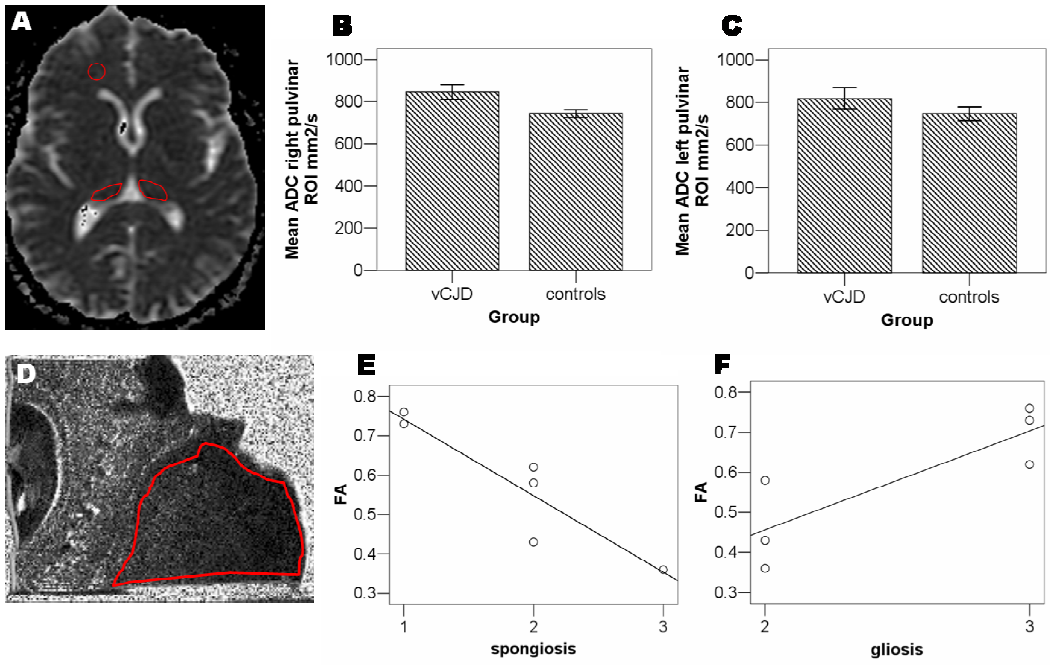
Introduction: Variant Creutzfeldt-Jakob disease (vCJD), known to be caused by the same prion strain as that causing Bovine Spongiform Encephalopathy (BSE),[1] is a uniformly fatal disease which remains a significant public health issue. The WHO criteria for diagnosis of vCJD include the "pulvinar sign": symmetrical bilateral thalamic high signal on T2W and FLAIR with sensitivities of 78-100%[2,3]. The neuropathological significance of the pulvinar sign remains uncertain. Diffusion-weighted imaging (DWI) is sensitive to changes in tissue microstructure and may offer objective markers for early diagnosis and monitoring in vCJD. The aim of this study was to compare *in-vivo* pulvinar apparent diffusion coefficients (ADCs) obtained in vCJD patients and controls, and to correlate *ex-vivo* diffusion tensor imaging (DTI) results with histopathological scores.

Methods: With prior written consent from patients or families and local ethics committee approval, 8 patients with vCJD (3 female, 5 male, mean age 36.1 years, range 19-76) and 5 healthy volunteers (3 female, 2 male, mean age 41.2 years, range 33 - 52) underwent echo-planar DWI (b1000, TE101ms) in addition to conventional T2W and FLAIR imaging at 1.5T. Mean region-of-interest (ROI) ADCs for the pulvinar bilaterally, and right frontal white matter (a control region) were determined (see Fig.A). Excised formalin-fixed pulvinar and frontal lobe specimens from 6 of the patients underwent high resolution DTI at 9.4T. Diffusion was measured along six nonlinear co-directions (*b* factor of 1000 s/mm^2,TR 2000 ms,TE 22 ms). Maps of mean diffusivity (MD) and fractional anisotropy (FA) were calculated and ROIs drawn in the pulvinar nucleus (see Fig D), frontal grey and frontal white matter. Histological processing including immunohistochemistry was performed and the degree of gliosis, spongiosis and prion protein deposition in the pulvinar and frontal white matter were scored from 0-3 (3 most severe). The Mann-Whitney U test was used to assess differences between groups and Spearman rank correlation to assess relationships between DTI and histological measures.

Results: All patients exhibited the pulvinar sign on conventional imaging and pulvinar signal hyperintensity on b1000 diffusion-weighted images. *In-vivo* ADCs in the pulvinar were significantly higher in patients with vCJD than healthy volunteers (right: p=0.001, Fig B; left: p=0.028, Fig C). There was no significant frontal white matter ADC difference between the patient and control groups. Correlations between *ex vivo* DTI measures and histopathological scores were significant for FA and spongiosis (r=-0.926, p=0.008, Fig E) and FA and gliosis (r=0.878, p=0.021, Fig F). No significant associations between MD and the histological measures were observed *ex vivo*. Significantly higher histological scores for gliosis (p=0.008), but not spongiosis or prion protein deposition in the pulvinar compared to the frontal grey matter ROIs were noted.



Conclusion: Despite the hyperintensity seen on DWI, *in vivo* pulvinar ADCs were increased in vCJD compared with controls, suggesting that this pulvinar hyperintensity is a T2 effect, while histological analysis demonstrated that gliosis in the pulvinar is likely to be the pathological substrate. Correlations between *ex vivo* FA and histopathological scores were negative for spongiosis and positive for gliosis, suggesting the latter may reinforce the directional organization of the neuropil. Future studies will determine the value of i*n vivo* DTI metrics as pathologically specific indices of disease severity in vCJD.

References:

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