Regional and Global Apparent Diffusion Coefficient in Inherited Prion Diseases: Correlation with Disease Severity

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Introduction

Inherited prion diseases, also known as familial Creutzfeldt-Jakob diseases, are progressive neurodegenerative conditions caused by different mutations within the prion protein (*PRNP*) gene[1]. Although appearances on conventional MR sequences are often unremarkable, cerebral diffusion weighted imaging (DWI) has recently emerged as the most sensitive sequence for the diagnosis of prion diseases [2,3] with reports of apparent diffusion coefficient (ADC) changes in specific anatomical regions [4,5]. The purpose of this study was to determine regional and global changes in cerebral ADC in a large cohort of these patients, and by correlation with clinical neurological indices investigate their potential as biomarkers of disease progression..

Methods

Twenty five patients (11 male, 14 female, mean age 45.2 years, range 32-69 years) with inherited prion disease underwent echo-planar diffusion-weighted imaging (b1000, TE101msin addition to conventional T2W and FLAIR sequences at 1.5T (GE Medical Systems, Milwaukee, WI). Mean region-of-interest (ROI) ADCs for the head of caudate, putamen and pulvinar nuclei were determined bilaterally and volume-normalised whole-brain ADC histograms computed following tissue segmentation using validated software[6]. Each patient was assessed with the neurological rating scales: Mini Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale (ADAS-COG), Clinician's Dementia Rating (CDR) and the Rating of Global Severity (GS). The Spearman rank correlation coefficient was calculated for each of the ROI mean ADCs, the whole-brain mean and median ADCs, and histogram peak height and peak position, versus clinical score, with $p<0.01$ accepted as significant.

Results

Significant correlations were found between whole-brain mean ADC, median ADC and histogram peak height and each of the clinical scores. For the whole-brain measures, the strongest correlations were with MMSE (MMSE score *decreases* with disease severity): whole-brain mean ADC vs. MMSE: r=-0.59, p=0.002 (Fig 1), whole-brain ADC histogram peak height vs. MMSE: r=0.62, p=0.001 (Fig 2) and median whole-brain ADC vs. MMSE: r=-0.58, p=0.003). Of the ROIs investigated, bilateral pulvinar mean ROI ADCs alone correlated significantly with each of the clinical scores, the most significant correlations being between the pulvinar mean ADC and ADAS-COG (ADAS-COG score *increases* with disease severity): right: r=0.78, p<0.001 (Fig 3) and left: r=0.78, p<0.001 (fig 4)). No pathological signal changes were detected on conventional MR imaging.

Discussion and Conclusion

Both anatomically specific and whole-brain ADC metrics correlated with disease severity in patients with inherited prion disease. ADC is sensitive to the microscopic structure of brain tissue and elevated values have been reported in patients with other neurodegenerative diseases[7]. Neuronal loss, in addition to gliosis, spongiosis and prion protein deposition are histopathological features of prion disease with a predeliction for the grey matter[8]. ADAS-COG is a clinical measure that covers a broader range of cognitive domains than MMSE, and the stronger correlation between mean pulvinar ADC and ADAS-COG may therefore reflect specific cognitive functional deficits related to injury in this location. Conventional MR imaging, including visual assessment of DWI, was relatively insensitive to cerebral pathology in this patient group. Despite this, we have shown that quantification of cerebral ADC provides both regional and global measures that correlate with clinical neurological status and therefore show promise as quantitative pathological biomarkers in inherited prion disease.

Fig 1: Mean whole-brain ADC versus MMSE, r=-0.59

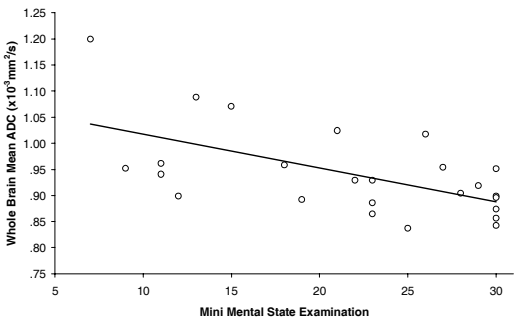


Fig 2: ADC histogram peak height versus MMSE, r=0.62

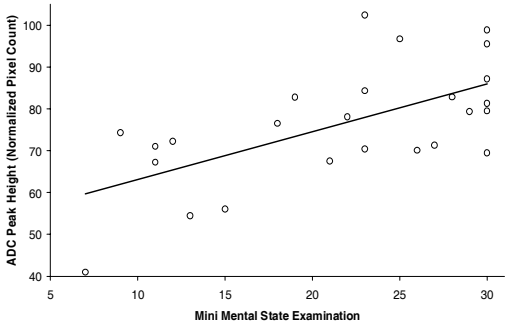


Fig 3: Right pulvinar ADC versus ADAS-COG, r=0.78

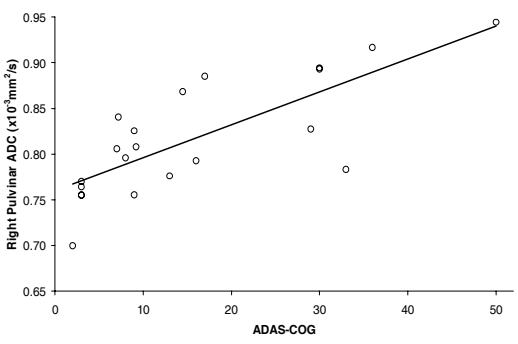
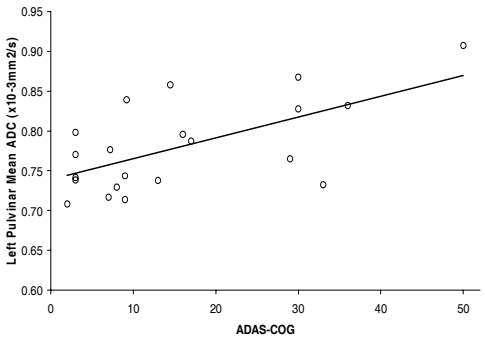


Fig 4: Left pulvinar ADC versus ADAS-COG, r=0.78



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