ADC and proton spectroscopy reflect cellular pathology in patients with Creutzfeldt-Jakob disease

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Introduction

Sporadic Creutzfeldt-Jakob disease (sCJD) is the most commonly occurring form of prion diseases, a group of rare, fatal neurodegenerative disorders associated with the accumulation of mis-folded PrP protein. Although diagnostic criteria for each form have been published [1], the course of the disease is uncertain and consequently radiological investigations often appear atypical. The current work is part of an on-going study[§] to evaluate the relationship between MRI and MRS markers of disease progression and the underlying pathology demonstrated *post mortem*.

Methods

Over a three year period 14 patients presenting as possible or probable prion disease [1] were recruited, and scanned with a combined MRI/MRS protocol [2,3]. Of these, four (2 female, age 60±11 yrs) died as a result of the disease and diagnosis has subsequently been confirmed by autopsy. A group of 19 age/sex-matched healthy controls was also studied by the MR protocol, although not all scans were acquired for every subject.

MR studies were performed using a 1.5T GE Signa Horizon LX whole body scanner and 25 cm diameter quadrature birdcage coil.

MRI. After anatomical imaging of the brain (axial T2-weighted FLAIR, 20 - 24 slices with FOV 24x24 cm and 6mm slice separation), diffusion-weighted EPI was run on the same slice locations, with a 192x192 matrix, TE 98.8 ms, TR 10 sec, b = 0, 900 mm/s, either in 3 or 6 axes. For each slice, images of apparent diffusion coefficient (ADC) and T2-weighting (T2W) were generated, and mean values calculated for brain areas of interest as described below. ***^{1}H-MRS.*** Voxels were selected in the thalamic nuclei, cerebellum, parietal-occipital cortex and striatum; spectra were acquired using the PRESS single voxel localisation sequence (TE=35 ms; TR= 4000 ms). Peak areas for NAA, creatine-phosphocreatine (Cr) and choline (Cho) were calculated using the time-domain fitting program AMARES/MRUI. Peak integral values were expressed relative to the Cr peak. ***Histology***. Brains were fixed shortly after the patients' decease (1-19 months after MR examination) and histological studies were performed. 9 brain areas were studied of which 4 are reported here (medial thalamus, hemispheric cerebellum, calcarine cortex and striatum). Each area was rated on an established semi-quantitative scale [4], for degree of spongiform changes (Sp), reactive gliosis (Gl), and neuronal loss (NL) determined by hematoxylin-eosin staining. ***Analysis.*** Healthy controls were assumed to score zero on histological assessment, after accounting for age-related effects. For patients and controls MR parameters were correlated with histological measures for each of the four brain areas studied by each modality. Statistical significance was determined by the Student *t* test for unpaired data. Partial linear regression was then performed on areas showing significant correlations, based on the hypothesis that detected changes in ADC or metabolite ratios might be accounted for by alterations in tissue micro-structure.

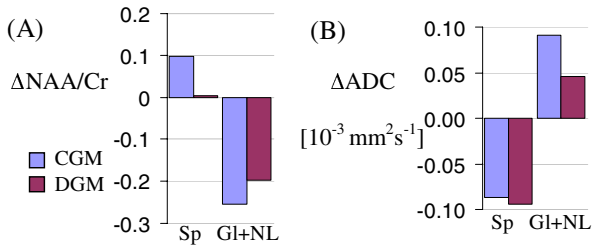
Results

Analysis of histological data shows Gl and NL to be highly correlated in all brain areas studied, and consequently they were treated as a single variable Gl+NL. The NAA/Cr ratio correlated with histological parameters in all brain areas (Table), while no such relationship was found for the Cho/Cr ratio. Likewise ADC was correlated to histological parameters in all areas, while no consistent relationship was found between T2-weighting and histology (data not shown).

To clarify the relationship between histology and MR parameters, data were grouped into deep grey matter (DGM = striatum + thalamus) and cortical grey matter (CGM = occipital cortex + cerebellar cortex), and partial regression was performed. Results are shown in Figures A and B. ADC increased with gliosis and loss of neurons, but decreased with increasing spongiosis. NAA was reduced relative to Cr with increasing neuronal loss/gliosis. The effect of spongiosis on NAA/Cr was equivocal, being negligeable in the cortical ROIs and apparently positive in DGM.

Table. Correlations between MR measurements and histological findings. Sig. p<5%* p<1%**

	NAA/Cr		ADC	
Brain area	Sp	Gl+NL	Sp	Gl+NL
Cerebellar cortex	-0.72**	-0.84**	+0.61	+0.73*
Occipital cortex	-0.83**	-0.84**	-0.86**	-0.82**
Striatum	-0.78*	-0.75*	-0.95**	-0.94**
Thalamus	-0.34	-0.95**	-0.84**	+0.28



Figures Change in (A) NAA/Cr ratio and (B) ADC for unit increase in histology measure Sp or Gl+NL of deep (DGM) and cortical (CGM) grey matter, determined by partial regression.

Discussion

The parallel processes of neuronal loss and reactive gliosis are reflected in the MR data as an increased ADC and relative reduction in NAA (a putative neuronal marker). Consistent with previous suggestions [2,5], spongiosis appears to restrict water diffusion, without reducing the proportion of cells containing NAA. For each brain area, observed correlations depend on the relative strength of these factors.

References

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