Longitudinal Short Echo Time Proton Magnetic Resonance Spectroscopy as a Biomarker in Patients with Inherited Prion Diseases

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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]. Conventional MR appearances are often unremarkable in these patients but with a therapeutic trial underway, non-invasive monitoring of disease progression is vital. To date, proton magnetic resonance spectroscopy (^{1}H-MRS) studies in inherited prion disease have been limited to case reports and small series[2-4]. The purpose of this study was to determine longitudinal changes in cerebral ^{1}H-MRS metabolite-ratios in inherited prion disease and investigate their value as surrogate markers of disease progression.

Methods

Five symptomatic patients (3 male, 2 female, mean age 46 years) with inherited prion disease, referred to the UK National Prion Clinic, National Hospital for Neurology and Neurosurgery, and treated with quinacrine under the MRC Prion 1 Trial, were studied. Short echo time (TE), single voxel ^{1}H-MRS was performed using an automated point-resolved spin-echo localisation (PRESS) technique, with TE 35ms, TR 3000, NEX 8 at 1.5T (GE Medical Systems, Milwaukee, WI). Spectra were acquired from two voxels (volume 3.3ml-4.4ml) centred on the right head of caudate (RHC) to include the anterior right putamen, and the right thalamus (RTH) (Fig 1). Signal ratios for the metabolites N-acetylaspartate (NAA), choline containing compounds (Cho) and *myo*-inositol (MI) relative to total creatine (Cr) were determined using LCModel software[5]. Spectra were obtained serially using the same protocol in all patients at 3 month intervals to a maximum of 9 months follow up and linear regression used to explore the change in metabolite ratios with time from baseline.

Results

Clinically all patients demonstrated disease progression with a decrease in Mini Mental State Examination (MMSE) and Activities of Daily Living (ADL) clinical scores. Appearances on conventional MRI were unremarkable except for mild volume loss. In the RHC voxel, all patients demonstrated a decrease in NAA/Cr and an increase in MI/Cr with time (Figs. 2 and 3). Linear regression analysis yielded a mean slope of -0.0520 (SE 0.013) per month versus time for NAA/Cr (p=0.018) and 0.0975 (SE 0.025) per month versus time for MI/Cr (p=0.018). No significant change with time was seen for Cho/Cr in the RHC voxel, or any metabolite-ratio investigated in the RTH voxel.

Discussion and Conclusions

Anatomically specific changes in NAA/Cr and MI/Cr were observed concomitant with clinical deterioration. Spongiosis, gliosis, neuronal loss and prion protein deposition (sometimes as amyloid plaques) are histopathological features of inherited prion disease and changes are often extensive in the caudate and putamen[6]. Elevated MI/Cr is thought to be associated with gliosis, and reduced NAA/Cr with neuronal loss in neurodegenerative conditions[7]. In the RHC voxel we observed a proportionally greater change in MI/Cr than NAA/Cr, suggesting that MI/Cr may be a more sensitive index of pathological change in this region.

In contrast to conventional MR imaging, longitudinal short-TE ^{1}H-MRS may provide important surrogate markers of disease progression in patients with inherited forms of prion disease.

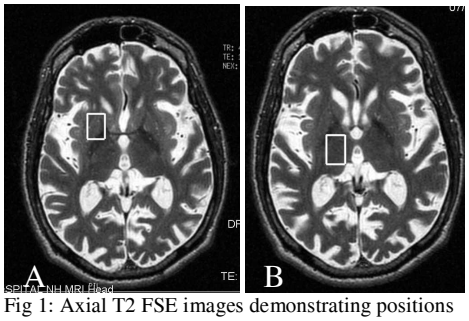

Fig 1: Axial T2 FSE images demonstrating positions of the RHC voxel (A) and RTH voxel (B).

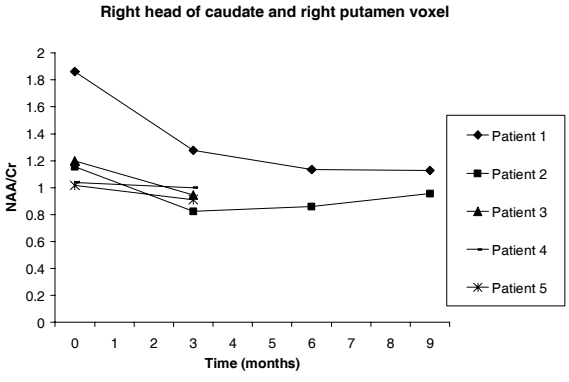

Fig 2: NAA/Cr versus time in RHC voxel

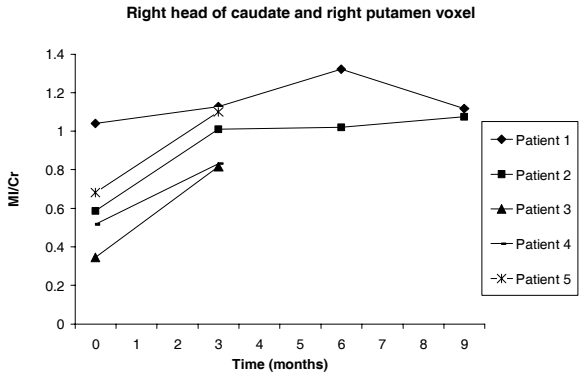

Fig 3: MI/Cr versus time in the RHC voxel

References

(1) Malluci G *et al.* Curr Opin Neurol. **17**(6), 641-647 (2004)
(2) Shyu W-C *et al.*. J Neurol Sci. **138**, 157-160 (1996)
(3) Konaka K *et al.* Neuroradiology. **42**, 662-665 (2000)
(4) Waldmann AD *et al.* Neuroradiology. **48**(6), 428-33 (2006)
(5).Provencher SW *et al.* Magn Reson Med. **30**, 672-679 (1993)
(6) Nicholl D *et al.* J Neurol Neurosurg Pyschiatry. **58**, 65-69 (1995)
(7) Valenzuela *et al.* Neurology. **56**, 592-598 (2001)

This project was funded by the Medical Research Council.