Abnormal ADC in the brain of prion disease patients: variation between brain structures

D. N. Manners[1], R. Lodi[1], P. Parchi[2], C. Tonon[1], S. Capellari[2], A. Filla[3], G. Pierangeli[1], C. Testa[1], P. Cortelli[2], P. Montagna[2], B. Barbiroli[1]

[1]Clinical Medicine and Biotechnology, University of Bologna, Bologna, Italy, [2]Neurological Sciences, University of Bologna, Bologna, Italy, [3]Neurological Sciences, Università Federico II, Napoli, Italy

Introduction

Prion diseases are rare, fatal neurodegenerative disorders whose most common forms are sporadic Creutzfeldt-Jakob disease (sCJD) and inherited forms such as fatal familial insomnia and Gerstmann-Sträussler-Schienker disorder (GSS). 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 combining MRI, MRS and pathology to better understand disease progression in CJD, and is aimed at evaluating an observer-independent method for assessing abnormalities in MRI images of these subjects.

Methods

Five prion patients (3F, 55±14 yrs) were recruited, and 6 age- and sex-matched controls (3F, 52±9 yrs). MRI was performed using a 1.5T GE Signa Horizon LX whole-body scanner and 25 cm diameter quadrature birdcage coil. After anatomical imaging of the brain (axial T2-weighted FLAIR, 20 - 24 slices with FOV 24x24 cm and 6 mm 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, three images were generated: a diffusion weighted (DWI) trace, an apparent diffusion coefficient (ADC) and T2-weighted (T2W) image.

Changes throughout the brain were examined. All regions of interest (ROIs) were defined directly on the EPI images, to avoid the difficulty of registration onto the structural scans. Analysis software was designed to determine regions of cortical grey matter (GM), white matter (WM) and CSF. The software uses a Bayesian procedure taking as prior knowledge information on local tissue distributions derived from the BrainWeb database [2], and an initial estimate of tissue signal intensity based on a k-means clustering of the T2W image. The result is an estimate of the fractional content of each tissue type in each pixel. Subsequently the cortex was divided by an automatic procedure into two ROIs, depending on the CSF content, and WM close to pixels with high CSF content was excluded from consideration.

Deep grey matter structures were outlined by hand. To reduce operator bias outlines were based on k-means clustering of both DWI and T2W images of deep brain grey/white matter. Group differences were assessed by the non-parametric Wilcoxon 2-sample test.

Results

Four patients had a confirmed *post mortem* pathological diagnosis (3 sCJD, 1 sporadic fatal insomnia (sFI)), while in the other case a genetic diagnosis of GSS was made (mutation P102L in the PRNP gene). Estimated ADC values for selected ROIs are summarised in Table 1, with the distribution of values shown in Figures 1 & 2. (Note that the sFI case was scanned two times, six months apart.) DWI findings were similar, with DWI hyperintensity corresponding to low ADC, but changes were not so clearly defined and are not presented. In the CJD group, values for the deep grey matter structures were lower than in controls, particularly in the caudate nucleus and putamen, with thalamus and globus pallidus appearing more normal. The sFI case showed increased ADC. Only the GSS patient had mean deep grey matter ADC values within the normal range. An average for deep grey matter is presented in the figures. In the WM ROI, including all pixels with an estimated white matter content >50%, not labelled as CSF or cortical or deep grey matter, ADC was above the normal range in both the CJD and sFI subjects. Heterogeneous cortical ADC changes were observed in some patients, but are not reported here.

Table 1. ADC values for subject groups. (* Significant difference with respect to controls at $p < 0.05$. † Mean of 2 scans)

Subjects	Age (yrs)		ADC ($x10^{-3}$ mm^2/s)	
	n	(mean ±SD)	WM	Deep grey matter
Control	6	52 ± 9	0.756 ± 0.033	0.755 ± 0.010
CJD	3	64 ± 7	*0.809 ± 0.073	*0.672 ± 0.065
sFI	1†	45	0.826	0.839
GSS	1	36	0.748	0.756

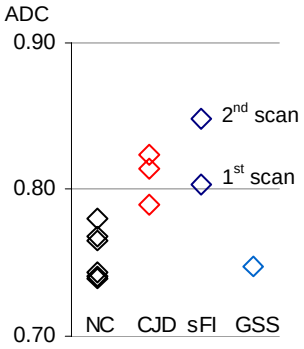

Figure 1. ADC ($x10^{-3}$ mm^2/s) for individual cases in WM ROI

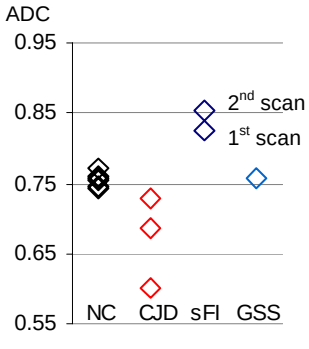

Figure 2. ADC ($x10^{-3}$ mm^2/s) for individual cases in combined deep grey matter ROIs

Discussion

Increased DWI (and reduced ADC) is a frequently reported radiological indication in prion diseases. This was observed in our CJD cases but not in the sFI, scanned on two separate occasions (12 and 18 months after presentation of symptoms), where ADC was higher on the second occasion. In contrast, WM diffusion was seen to increase in all the patients except the GSS case, even those presenting with short disease duration. The pattern of involvement of different brain areas is currently being investigated.

Together these finding suggest that two processes are operating, one leading to decreased diffusion (and the previously observed [3] deep grey matter DWI hyperintensity) and a second increasing ADC in the longer term, which is first observed in white matter. These may correspond respectively to spongiosis (which is confined to deep grey matter, and does not occur in sFI) and neuronal/axonal loss [4]. In GSS, where disease progression is much slower, ADC changes were not observed.

Conclusions

Radiological presentation is known to be heterogeneous in prion diseases, and this is reflected in our study. ADC values of deep grey matter structures were high in sFI, while being lower than normal in CJD. Careful separation of brain regions allowed a significant increase in white matter ADC to be observed in all the non-genetic prion patients scanned. Future investigations in this on-going study will test the generality of these findings.

References

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