Global and Tissue-specific Cerebral Magnetisation Transfer Ratios in Inherited Prion Disease: Correlation with Disease Severity

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Introduction:

Inherited Prion Diseases (IPDs) are rare, progressive neurodegenerative disorders caused by mutations within the prion protein (PRNP) gene[1] and are uniformly fatal. Cerebral magnetisation transfer (MT) MR has been shown to be a sensitive marker of pathological change in conditions such as Multiple Sclerosis[2], prior to development of signal abnormalities on conventional MR. Conventional MR can often be unremarkable in IPD, and the purpose of this study was to assess global and regional changes in Magnetisation Transfer Ratio (MTR) derived from MT MR, and by correlation with clinical neurological indices to investigate the potential of MTR as a quantitative biomarker of disease severity in IPD.

Methods:

Twenty-three patients (12 male, 11 female, mean age 45.5 years, range 32-59 years) with IPD, recruited into the MRC Prion-1 Trial, were included. They underwent MT and conventional DWI and FLAIR imaging, at 1.5 T (GE Healthcare). Following image segmentation using FSL (www.fmrib.ox.ac.uk/fsl), whole brain, white matter and grey matter MTR histograms were computed and for each, mean MTR (AVMTR), peak height (PH), peak location (PL), and MTR at the 25th, 50th and 75th percentile (MTR25%, MTR50%, MTR75%) were calculated. Patients were assessed using videoed (cognitive, extrapyramidal, pyramidal and cerebellar impairment) and non-videoed neurological rating scales (Clinician's Global Impression of disease Severity (CGIS), Clinician's Dementia Rating (CDR), Alzheimer's Disease Assessment Scale (ADAS-COG), Activities of Daily Living (ADL), Brief Psychiatric Rating Scale (BPRS), Mini Mental Score Examination (MMSE) and Rankin scores. Spearman rank correlation was used to assess the relationship between MTR measures and each clinical score, with $p \leq 0.01$ considered statistically significant.

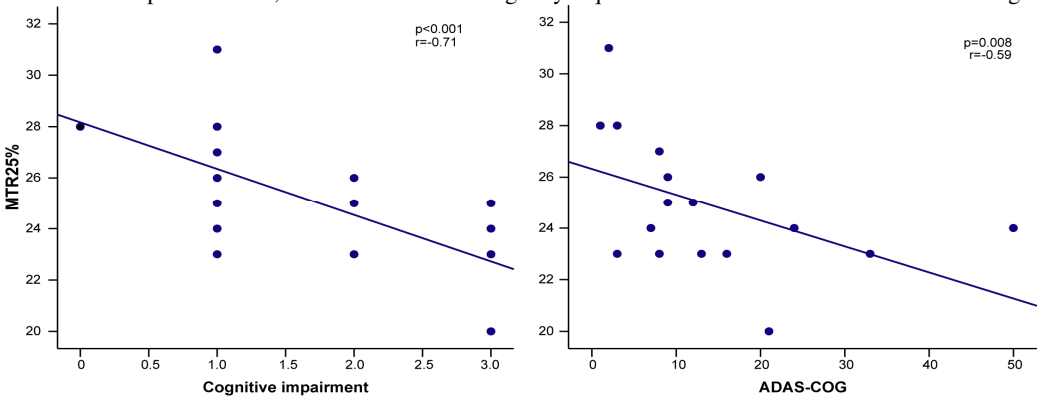
Results:

In general, whole-brain and grey matter mean MTR decreased with disease severity. Significant correlations between MTR parameters and clinical scores are detailed in the table below. Only 1 patient had pathological signal change on conventional imaging.

MTR histogram measure		Clinical scores and Spearman p values
Whole brain	AVMTR	Cognitive impairment (p<0.001), Rankin (p=0.008), CDR (p=0.003), ADAS-COG (p=0.004)
	PH	Rankin (p=0.002)
	MTR25%	Cognitive impairment (p=0.001), MMSE (p=0.008), Rankin (p=0.001), CDR (p<0.001), ADAS-COG (p=0.008), CGIS (p=0.006)
	MTR50%	Rankin (p=0.004)
White matter	PL	Rankin (p=0.01)
	MTR25%	Rankin (p=0.01)
	MTR50%	Rankin (p=0.01)
	MTR75%	Cognitive impairment (p=0.01), ADAS-COG (p=0.004)
Grey matter	AVMTR	Cognitive impairment (p=0.002), Rankin (p=0.01), CDR (p=0.01), ADAS-COG (p=0.008)
	PH	Cognitive impairment (p=0.001), Rankin (p=0.003), CDR (p=0.003), CGIS (p=0.008)
	MTR25%	Cognitive impairment (p=0.002), Rankin (p=0.006), CDR (p=0.01)
	MTR50%	Cognitive impairment (p=0.003), ADAS-COG (p=0.01)
	MTR75%	ADAS-COG (0.008)

Conclusions:

For the first time we have demonstrated relationships between quantitative whole brain, white matter and grey matter MTR histogram measures and clinical status in patients with IPD. These correlations presumably reflect disruption of tissue microstructure in IPD, and were observed in the absence of significant changes on conventional MRI. MT MR may provide valuable objective and robust indices of IPD disease severity, and with the advent of therapeutic trials [3], such biomarkers are urgently required in order to monitor the effects of drug treatment on disease progression.



Relationships between whole brain MTR25% and cognitive impairment (p=0.001) and ADAS-COG scores (p=0.008)

References:

1. Mead S. Eur J HumGenet 2006.
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3. Wroe S, Journal of the Neurological Sciences 2005; 238: S1-S570

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