Distribution of diffusivity changes in subcortical deep gray matter in prion diseases

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Introduction

Human prion diseases (HPD) are rare, fatal, neurodegenerative disorders mainly affecting the central nervous system, which can be familial, sporadic or acquired by infection (1). The typical deposition of PrPSc, an abnormally folded, protease-resistant, beta-sheet rich isoform of a normal cellular prion protein, in the form of diffuse deposits or plaques is accompanied by the classic histological triad of spongiosis, gliosis, and neuronal loss. The variable pattern of increased brain signal intensity on diffusion weighted images (2) in different forms of HPD has been linked to the different distribution of spongiosis (3) that results in restricted diffusivity and increased signal intensity in diffusion-weighted images. In the present study we investigated mean diffusivity changes in deep gray matter structures of patients with different types of prion diseases, some of them characterised by little or absent brain spongiosis.

Methods

Nine consecutive patients (2 females, 36-79 years, age range, 61±16 years, mean ±SD) with probable or possible prion disease (2) were recruited. Twelve sex- and age-matched healthy subjects (3 females, 40-83 years, 59±11 years, mean ±SD) were also studied. For all recruited patients, CSF samples were analyzed for the presence of the 14-3-3 protein, and a genetic study of the human prion protein gene was carried out. A post-mortem examination was performed in 5 patients.

MR acquisition. MR studies were performed using a 1.5T GE Signa Horizon LX whole body scanner and 25 cm diameter quadrature birdcage coil. T1-weighted FSE and T2-weighted FLAIR axial images was acquired with 4 mm slice thickness, along with DTI SE-EPI images encoded in 6 directions, at the same slice spacing. **Data analysis**. Diffusivity and FA maps were generated using tools provided by FMRIB/FSL (4). Automatic segmentation of sub-cortical grey matter structures (see Table) was performed in three stages. Firstly, the MNI FA template was registered onto subjects' own FA map using non-linear registration (flirt+fnirt, FMRIB/FSL). Deep grey structures were identified by warping the Harvard-Oxford sub-cortical structure atlas, using the same deformation field. White matter partial volume was excluded using an FA threshold optimized for each structure, while CSF was excluded by eliminating pixels with diffusivity > 1.25×10^{-3} mm^2 s^{-1}. For each structure right-left mean was calculated. Group differences in MD for each deep gray matter structure were determined by the Student *t* test for unpaired data. Differences in variance between patients and controls were tested using the variance ratio F-test. Group data are reported as mean ±SD.

Table — Mean diffusivity ($\times 10^{-3}$ mm^2/s)

Group		Caudate	Pallidus	Putamen	Thalamus	Hippocampus	Amygdala
Prion patients (n=10)		0.71 ± 0.11	0.76 ± 0.07	0.66 ± 0.13	0.76 ± 0.09	0.92 ± 0.03	0.88 ± 0.04
Controls (n=12)		0.79 ± 0.02	0.75 ± 0.03	0.76 ± 0.02	0.79 ± 0.03	0.90 ± 0.04	0.86 ± 0.04
Student t test	***p***	*0.02*	*0.86*	*0.01*	*0.21*	*0.13*	*0.21*
Variance ratio test	***p***	*< 0.001*	*0.01*	*< 0.001*	*< 0.001*	*0.45*	*0.65*

Results

A definite diagnosis of either sporadic CJD (sCJD) or genetic prion disease was made in six patients. Among these patients, four had a final diagnosis of definite sporadic CJD (sCJD) (2 VV2, 1 MV2, and 1 MM1 patient), one of Familial Fatal Insomnia (FFI) and one of Gerstmann-Sträussler-Scheinker (GSS). In three patients (one still alive with a MV genotype) and two (MM and VV genotypes) deceased without post-mortem examination all positive for the 14-3-3 protein, the final diagnosis was of probable CJD. MD values were significantly reduced only in the caudate and putamen (Table). However, group variance was statistically different between patients and controls in the basal ganglia and thalamus. The Figure shows that increased variance is associated with different sub-types of prion diseases. FFI and GSS patients tended to have MD values above the normal range in basal ganglia and thalamus while all the sCJD subtypes showed reduced MD values in the caudate. Reduced MD values in the thalamus were mostly associated with the homozygous VV subtype.

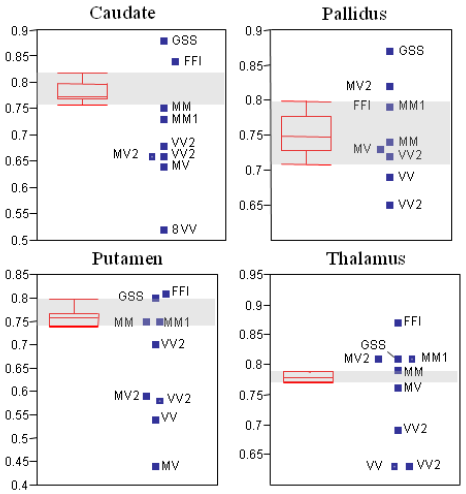

Figure. Distribution of MD ($\times 10^{-3}$ mm^2/s) in controls (boxplot) and patients (labelled points) in deep grey matter ROIs. Box shows interquartile range divided by median; whiskers extend to extreme values.

Discussion

In this study we investigated changes in MD values of deep gray matter structures, obtained using a completely operator-independent method, in different sub-types of prion disease patients. In forms like FFI and GSS where there is little or no spongiosis (1) MD values were increased as in other neurodegenerative disorders (5). In contrast, MD values were variably reduced in basal ganglia of different sCJD sub-types all characterized by the presence of spongiosis (6). MD values were severely reduced in the thalamus of VV homozygous sCJD patients.

References

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