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Application of quantitative DTI metrics in sporadic CJD ☆

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ABSTRACT

Diffusion Weighted Imaging is extremely important for the diagnosis of probable sporadic Jakob–Creutzfeldt disease, the most common human prion disease. Although visual assessment of DWI MRI is critical diagnostically, a more objective, quantifiable approach might more precisely identify the precise pattern of brain involvement. Furthermore, a quantitative, systematic tracking of MRI changes occurring over time might provide insights regarding the underlying histopathological mechanisms of human prion disease and provide information useful for clinical trials. The purposes of this study were: 1) to describe quantitatively the average cross-sectional pattern of reduced mean diffusivity, fractional anisotropy, atrophy and T1 relaxation in the gray matter (GM) in sporadic Jakob–Creutzfeldt disease, 2) to study changes in mean diffusivity and atrophy over time and 3) to explore their relationship with clinical scales. Twenty-six sporadic Jakob–Creutzfeldt disease and nine control subjects had MRIs on the same scanner; seven sCJD subjects had a second scan after approximately two months. Cortical and subcortical gray matter regions were parcellated with Freesurfer. Average cortical thickness (or subcortical volume), T1-relaxiation and mean diffusivity from co-registered diffusion maps were calculated in each region for each subject. Quantitatively on cross-sectional analysis, certain brain regions were preferentially affected by reduced mean diffusivity (parietal, temporal lobes, posterior cingulate, thalamus and deep nuclei), but with relative sparing of the frontal and occipital lobes. Serial imaging, surprisingly showed that mean diffusivity did not have a linear or unidirectional reduction over time, but tended to decrease initially and then reverse

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and increase towards normalization. Furthermore, there was a strong correlation between worsening of patient clinical function (based on modified Barthel score) and increasing mean diffusivity.

1. Introduction

Sporadic Jakob–Creutzfeldt disease (sCJD) is unique among neurodegenerative diseases as there is an MRI marker (restricted diffusion of certain gray matter regions) with very high sensitivity and specificity (Meissner et al., 2009; Vitali et al., 2011; Young et al., 2005). Most prior MRI studies in sCJD studying cortical restricted diffusion have been performed by a visual assessment analysis on fluid-attenuated inversion recovery (FLAIR) and/or diffusion weighted images (DWI) sequences (Meissner et al., 2009; Tschampa et al., 2007; Vitali et al., 2011; Young et al., 2005). Due to MRI susceptibility and other artifacts, this "qualitative" approach, however, may not show the extent of true brain involvement (Lin et al., 2006). Improved understanding of the quantification and pattern of brain MRI changes that occur in sCJD (such as atrophy and diffusion) (Cohen et al., 2009; Lee et al., 2012; Wang et al., 2013) as well as their changes over time might provide important biomarker data to track for future clinical trials, as well as provide insights on mechanisms of the disease and prion spread. Tracking MRI progression in other neurodegenerative diseases has usually been done by following structural measures of white or gray matter integrity or metabolism; such studies have consistently reported a roughly linear or unidirectional decline (Driscoll et al., 2009; Shiga et al., 2004). Additionally, it is not clear what happens with restricted diffusion over time in sCJD (Geschwind et al., 2009; White et al., 2003). To our knowledge, there have been no formal studies on the course of DWI overtime in human prion disease, only case reports. Some case reports suggest increasing DWI involvement (Kono et al., 2011; Ukisu et al., 2005), whereas others suggest less DWI involvement, particularly with atrophy (Matoba et al., 2001; Tribl et al., 2002).

Although diffusion tensor imaging (DTI) has emerged as a sensitive diagnostic technique highlighting mean diffusivity (MD) abnormalities in the gray matter (GM) in human prion diseases, few studies quantified MD and fractional anisotropy (FA) abnormalities and none have examined regional and whole brain MD and FA both cross-sectionally and longitudinally in a cohort of sCJD patients (Andrews, 2010; Fulbright et al., 2006; Manners et al., 2009; Ukisu et al., 2005; Wang et al., 2013). Our aims were 1) to describe quantitatively the average pattern of reduced MD, FA, atrophy and T1 relaxation in the gray matter (GM) in sCJD as well as 2) to determine the changes of mean diffusivity and atrophy over time and 3) their relationship with clinical scales in a sub-cohort with serial imaging.

2. Material and methods

2.1. Subjects

All subjects or their designees provided informed consent for participation in this study, which was approved by our institutional review board. Subjects were evaluated between August 2005 and August 2008 at the University of California of San Francisco (UCSF) Memory and Aging Center. We analyzed all serial sCJD subjects who had the same MRI protocol of adequate quality MRI (n = 26; mean age 62, SD ±9; 46% female). Twenty-three of 26 sCJD subjects (88%) had brain autopsy and were ultimately pathologically-proven sCJD (Table 1) (Kretzschmar et al., 1996); the three other subjects eventually met UCSF 2007 (Geschwind et al., 2007) and either WHO, 1998 or European probable sCJD criteria (WHO, 1998; Zerr et al., 2009). MRIs from nine healthy age and gender matched subjects were used as controls (mean age 62 (SD ±16) 44% female). Seven sCJD subjects had a second, serial brain MRI after about two months (2.17, SD ±0.23 months).

All sCJD subjects had a Mini-Mental State examination (MMSE), the modified Barthel index, the Neuropsychiatric Inventory total score (NPI; to assess the behavioral impairments) (Cummings, 1997) and detailed standardized neurological examination (±3 days from MRI scan date) (See Supplemental data and Table 1). For cases with pathology, prion typing was performed by the National Prion Disease Pathology Surveillance Center (NPDPSC; Cleveland, OH). Prion gene, *PRNP*, analysis for mutations and codon 129 polymorphisms done through the NPDPSC. All but one sCJD subjects were tested for *PRNP* mutations; this subject was not pathologically-proven, but had no family history of neuropsychiatric disorder and presented clinically as sCJD.

2.2. Imaging acquisition

Images were acquired on a 1.5 T GE Signa scanner. The acquisition protocol consisted in two axial T1-weighted 3D IRSPGR (axial slab with 60 slices of 3 mm thickness, TR/TE = 27/6 ms, in-plane matrix 256 × 256 covering a FOV of 24 × 24 cm^2 flip angle 40° and 8°), an axial T2 FLAIR (48 slices of 3 mm thickness, TR/TE/TI = 8802/122/2200 ms, 512 × 512 matrix with a FOV of 24 × 24 cm^2), and a DTI acquisition (15 non-collinear gradient directions with b = 1000 s/mm^2, one b = 0 reference image, 35 contiguous slices of 3 mm thickness, TR/TE = 12,400/69 ms, 128 × 128 matrix covering a FOV of 25.6 × 25.6 interpolated to give a final 1 × 1 × 3 mm^3 resolution). Due to acquisition windowing problems, information on the inferior temporal lobe (entorhinal, fusiform, inferiotemporal, middletemporal, temporal pole ROIs) was lost for three subjects.

2.3. Imaging analysis

The two T1-weighted 3-D inversion recovery-spoiled images (40 and 8°) were used to calculate the T1 relaxometry maps (T1R). FreeSurfer Image Analysis Suite 4.5 version (http://surfer.nmr.mgh.harvard.edu/) (Dale et al., 1999; Fischl et al., 1999) was used for cortical reconstruction, volumetric segmentation, subcortical (Fischl et al., 2004) and cortical parcellation (Desikan-Kyliany Atlas: 40 VOIs per hemisphere with Freesurfer Atlas), as well as determining cortical thickness in each VOI and deep nuclei volumes. Volumes were normalized for intracranial volume (Desikan et al., 2006). Segmentation results were assessed by an experienced operator to ensure accuracy.

Mean diffusivity and fractional anisotropy (FA) maps were calculated after eddy current and head motion correction. DTI data were corrected by applying an affine alignment of each image to the first no diffusion weighted (b0) image using the Oxford FSL toolkit (http://www.fmrib.ox.ac.uk/fsl/fdt/index.html). DTI maps were registered to the T1-weighted images. To decrease the potential effect of partial volume averaging, the Freesurfer mask of CSF was applied to exclude voxels that were likely to contain a mixture of CSF with GM from the VOI boundary. Averages were calculated for MD, FA, T1R, and thickness or volume for each VOI.

2.4. Statistical analysis

2.4.1. Cross-sectional analysis

Age-corrected Z-scores were used in the Mann–Whitney *U* test to compare the differences between the subjects and controls for MD, FA, T1R, cortical thickness and subcortical volumes (volumes corrected for intracranial volume). The Spearman non-parametric test was used to assess the correlation between the diffusion and volumetric parameters and the clinical data of the patients, as well as correlation test between MD and thickness Z-scores. False discovery rate (FDR) adjustment was