NeuroImage: Clinical 16 (2017) 595–603

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Longitudinal white matter change in frontotemporal dementia subtypes and sporadic late onset Alzheimer's disease

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ARTICLE INFO

Keywords:
Longitudinal
DTI
White matter integrity
Sample size
Clinical trial
FTD
AD
Behavioral variant FTD
Primary progressive aphasia

ABSTRACT

Background: Degradation of white matter microstructure has been demonstrated in frontotemporal lobar degeneration (FTLD) and Alzheimer's disease (AD). In preparation for clinical trials, ongoing studies are investigating the utility of longitudinal brain imaging for quantification of disease progression. To date only one study has examined sample size calculations based on longitudinal changes in white matter integrity in FTLD.
Objective: To quantify longitudinal changes in white matter microstructural integrity in the three canonical subtypes of frontotemporal dementia (FTD) and AD using diffusion tensor imaging (DTI).
Methods: 60 patients with clinical diagnoses of FTD, including 27 with behavioral variant frontotemporal dementia (bvFTD), 14 with non-fluent variant primary progressive aphasia (nfvPPA), and 19 with semantic variant PPA (svPPA), as well as 19 patients with AD and 69 healthy controls were studied. We used a voxel-wise approach to calculate annual rate of change in fractional anisotropy (FA) and mean diffusivity (MD) in each group using two time points approximately one year apart. Mean rates of change in FA and MD in 48 atlas-based regions-of-interest, as well as global measures of cognitive function were used to calculate sample sizes for clinical trials (80% power, alpha of 5%).
Results: All FTD groups showed statistically significant baseline and longitudinal white matter degeneration, with predominant involvement of frontal tracts in the bvFTD group, frontal and temporal tracts in the PPA groups and posterior tracts in the AD group. Longitudinal change in MD yielded a larger number of regions with sample sizes below 100 participants per therapeutic arm in comparison with FA. SvPPA had the smallest sample size based on change in MD in the fornix (n = 41 participants per study arm to detect a 40% effect of drug), and nfvPPA and AD had their smallest sample sizes based on rate of change in MD within the left superior longitudinal fasciculus (n = 49 for nfvPPA, and n = 23 for AD). BvFTD generally showed the largest sample size estimates (minimum n = 140 based on MD in the corpus callosum). The corpus callosum appeared to be the best region for a potential study that would include all FTD subtypes. Change in global measure of functional status (CDR box score) yielded the smallest sample size for bvFTD (n = 71), but clinical measures were inferior to white matter change for the other groups.
Conclusions: All three of the canonical subtypes of FTD are associated with significant change in white matter integrity over one year. These changes are consistent enough that drug effects in future clinical trials could be detected with relatively small numbers of participants. While there are some differences in regions of change across groups, the genu of the corpus callosum is a region that could be used to track progression in studies that include all subtypes.

1. Introduction

FTLD is a pathological term used to designate a group of neurodegenerative disorders that primarily affect the frontal and temporal lobes (Brun, 1987; Gorno-Tempini et al., 2011). FTLD is associated with a variety of clinical presentations, including three of the

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http://dx.doi.org/10.1016/j.nicl.2017.09.007
Received 14 March 2017; Received in revised form 17 August 2017; Accepted 6 September 2017
Available online 14 September 2017

most commonly described subtypes of FTD: bvFTD, nfvPPA, and svPPA (Johnson et al., 2005; Galantucci et al., 2011). These three syndromes differ in their clinical features, with bvFTD presenting primarily with changes in socioemotional function (Gorno-Tempini et al., 2011; Seeley, 2008; Garcin et al., 2009), svPPA with loss of knowledge about words, and objects, and nfvPPA with agrammatism, nonfluent speech and articulatory difficulties (Wilson et al., 2009; Wilson et al., 2010). Yet the three syndromes are linked by a relatively limited number of underlying proteinopathies. The two most common molecular pathologies include abnormal depositions of Tau or TDP-43 (TAR DNA-binding protein 43) (Neumann et al., 2006; Baborie et al., 2011). In some cases, the clinical syndrome strongly predicts the underlying pathology, as is the case with svPPA, which is associated with TDP-43 type C in about 83% of cases (Spinelli et al., 2017), or autosomal dominant genetic cases of bvFTD, such as *GRN* or *C9orf72* mutations, also associated with TDP-43 pathology. However, for the most part, clinico-pathological correlations continue to pose important diagnostic challenges. For instance, nfvPPA is often associated with tauopathy, although in certain cohorts a high frequency of TDP-43 pathology is reported [11,] (Boxer et al., 2006). The bvFTD clinical syndrome remains the most pathologically heterogenous subtype, caused most frequently by TDP-43 and tau pathologies, less frequently FUS, in addition to other more rare pathologies (Spinelli et al., 2017; Mann and Snowden, 2017; Munoz et al., 2009; Grossman, 2010).

As it stands, there are no approved therapies for FTLD, however efforts to develop treatments are ongoing (Zhang et al., 2016; Rojas and Boxer, 2016). In preparation for future clinical trials, efficient measures of disease progression that allow detection of drug effects with the smallest possible number of participants need to be developed. The heterogeneity in clinical presentations of FTLD proteinopathies makes this problem particularly complex. Future therapeutic trials will target specific proteinopathies. Therefore, once a biomarker is available to identify the proteinopathy for each case of FTLD *in vivo*, the ability to enroll any patient with the targeted protein disorder, irrespective of the specificity of their symptoms, would increase power. Drugs targeting tau, for instance, may include bvFTD and nfvPPA patients. In such trials, it would be difficult to choose an appropriate specific symptom-related outcome measure. Whereas language tasks may be appropriate for nfvPPA or svPPA, they would likely be insensitive to change in bvFTD within the optimal therapeutic window. Thus, in addition to global cognitive measures and assessment of functional abilities, there would be value in identifying quantifiable intermediate phenotypes, standing between the underlying molecular pathologies and clinical phenotypes. Such measures would be anticipated to be equally applicable to a variety of clinical syndromes, as well as perhaps especially needed for the study of specific subgroups, such as bvFTD patients with a slowly progressive, subcortical form of neurodegeneration (Ranasinghe et al., 2016).

Diffusion tensor imaging, which utilizes measures of water diffusion to assess microstructural alterations in white matter, has been used in cross-sectional and longitudinal assessment of white matter degeneration in FTD (Galantucci et al., 2011; Zhang et al., 2016; Acosta-Cabronero et al., 2011; Agosta et al., 2014; Borroni et al., 2007; Mahoney et al., 2015; Matsuo et al., 2008; Schwindt et al., 2013; Whitwell et al., 2010; Zhang et al., 2009; Lam et al., 2014; Floeter et al., 2016; Tu et al., 2016). This is consistent with pathological studies demonstrating that, in addition to neuronal cell death, FTLD brains also show substantial gliosis and degeneration of white matter tracts (Lant et al., 2014). Moreover, recent studies showed that longitudinal white matter changes over a 12 month period are more extensive than grey matter (Whitwell et al., 2010). Studies in bvFTD have demonstrated favorable effect sizes for white matter changes when compared to clinical or volumetric grey matter changes (Mahoney et al., 2015; Santillo et al., 2013). This suggests that longitudinal measures of white matter integrity may be excellent markers of pathological progression in FTLD.

The goal of this study was to quantify longitudinal changes in white matter integrity using DTI in bvFTD, svPPA and nfvPPA and to assess the utility of DTI as a metric of disease progression in each of these variants. In order to evaluate the specificity of the findings, we also examined longitudinal white matter changes in AD, a neurodegenerative disease affecting posterior rather than frontotemporal brain regions, with proteinopathies that differ from those noted in FTLD.

2. Methods

2.1. Participants

A total of 148 participants were included in this retrospective study. The study participants were individuals enrolled in ongoing longitudinal studies at the Memory and Aging Center at UCSF (MAC) who had undergone MRI twice approximately one year apart and were given the following diagnoses: bvFTD (n = 27), nfvPPA (n = 14), svPPA (n = 19), and AD (n = 19). Our control group was composed of participants who also had MRI scans approximately one year apart and were not given a diagnosis of neurodegenerative disease, and considered neurologically and cognitively normal (n = 69). Patients included in this study were recruited between 2008 and 2016 through ongoing studies (AG019724, AG032306, AG023501) at the MAC. Diagnoses were based on a multidisciplinary evaluation including neurological exam and symptomatic evaluation, neuropsychological and nursing evaluations, and socioemotional assessments. Disease duration was estimated based on the year of initial symptoms provided by the patient or their informant. All study participants were provided informed consent and the study protocols were approved by the UCSF Committee on Human Research. Research was performed in accordance with the Code of Ethics of the World Medical Association.

2.2. MRI acquisition

MR images were acquired on a 3 Tesla Siemens Tim Trio system equipped with a 12-channel head coil at the UCSF Neuroscience Imaging Center. Diffusion sequences were acquired using the following parameters: TR/TE 8200/86 ms; B = 0 image and 64 directions at B = 2000 s/mm^2; FOV 220 × 220 mm^2 and 2.2 mm thick slices; matrix 100 × 100 with 60 slices yielding 2.2 mm^3 isotropic voxels/(TR/TE 8000/109 ms; B = 0 image and 64 directions at B = 2000 s/mm^2; FOV 220 × 220 mm^2 and 2.2 mm thick slices; matrix 100 × 100 with 55 slices yielding 2.2 mm^3 isotropic voxels).

2.3. DTI processing

Processing of diffusion images was carried out using the FSL and Dipy utilities. The b = 0 image was co-registered to the diffusion direction images to create one 4D image followed by gradient direction eddy current and distortion correction. Diffusion tensors were calculated using a non-linear least-squares algorithm. To ensure our measurements were restricted to white matter tissue and not biased by atrophy, all data (both cross-sectional and longitudinal, ROI and voxel-based) was sampled from voxels which had a minimum FA value of 0.1 across all subjects.

2.4. Longitudinal registration

Longitudinal registration of diffusion data was accomplished through the DTI-TK software package (http://dti-tk.sourceforge.net) based on previously published methods: (http://www.sciencedirect.com/science/article/pii/S1053811913000918) (Keihaninejad et al., 2013). DTI-TK implements a tensor-based registration paradigm, maximizing the alignment of white matter structures and minimizing interpolation of DTI images. Intra-subject templates were created through iterative non-linear and linear registration of baseline and follow-up