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Widespread white matter and conduction defects in *PSEN1*-related spastic paraparesis

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ABSTRACT

The mechanisms underlying presenilin 1 (*PSEN1*) mutation–associated spastic paraparesis (SP) are not clear. We compared diffusion and volumetric magnetic resonance measures between 3 persons with SP associated with the A431E mutation and 7 symptomatic persons with *PSEN1* mutations without SP matched for symptom duration. We performed amyloid imaging and central motor and somatosensory conduction studies in 1 subject with SP. We found decreases in fractional anisotropy and increases in mean diffusivity in widespread white-matter areas including the corpus callosum, occipital, parietal, and frontal lobes in *PSEN1* mutation carriers with SP. Volumetric measures were not different, and amyloid imaging showed low signal in sensorimotor cortex and other areas in a single subject with SP. Electrophysiological studies demonstrated both slowed motor and sensory conduction in the lower extremities in this same subject. Our results suggest that SP in carriers of the A431E *PSEN1* mutation is a manifestation of widespread white-matter abnormalities not confined to the corticospinal tract that is at most indirectly related to the mutation's effect on amyloid precursor protein processing and amyloid deposition.

1. Introduction

Alzheimer's disease (AD) is the most common cause of neurodegenerative dementia, and an estimated 5.3 million Americans are currently afflicted by it (Alzheimer's, 2015). Of these persons, an estimated 200,000 are below age 65 (Alzheimer's, 2015), and a subset of these have autosomal dominant AD (ADAD). ADAD is an early-onset form of AD caused by the presence of essentially fully penetrant mutations in 1 of 3 genes; presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), or amyloid precursor protein (*APP*). The observation that pathogenic mutations in these genes affect cleavage of APP (Scheuner et al., 1996) is supportive evidence for a pivotal role of the β-amyloid (Aβ) protein in the etiology of AD (Hardy and Selkoe, 2002). Although increased relative or absolute production of the 42-amino acid length version of Aβ (Aβ42) has been reproducibly demonstrated in ADAD (Ringman et al., 2008), such overproduction is less evident in late-onset AD (LOAD). The prevailing hypothesis for the development of LOAD is a diminished ability to eliminate Aβ, leading to its aggregation and deposition (Tanzi et al., 2004). Despite this apparent difference, both LOAD and ADAD share pathologic features including neurofibrillary tangles (Ringman et al., 2016) and most often present with memory and executive deficits as well as personality changes (Ringman et al., 2011, 2015). However, a significant subset of persons with ADAD, particularly when due to *PSEN1* mutations, can have features atypical for AD including early myoclonus, pseudobulbar affect, and gait

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abnormalities due to spastic paraparesis (SP) (Joshi et al., 2012). SP can be the initial symptom, occur concurrently with, or somewhat after cognitive and behavioral changes in *PSEN1*-related ADAD and occurs in association with specific mutations (Karlstrom et al., 2008; Larner, 2013). The pathologic basis of SP and other clinical variants in *PSEN1*-related AD is controversial (Rudzinski et al., 2008; Yokota et al., 2003), and it is unclear whether it is related to qualitative or quantitative differences in APP processing, differences in the localization of resulting pathology (Martikainen et al., 2010) or other effects of *PSEN1* mutations (Xia et al., 2015).

The development of diffusion-weighted magnetic resonance imaging (MRI) has allowed for sensitive delineation of white-matter (WM) pathology in vivo (Bozzali et al., 2002; Medina et al., 2006). Diffusion-weighted imaging measures both the direction and magnitude of proton diffusion. Such diffusion can be characterized by overall magnitude (mean diffusivity or MD) and tendency for the diffusion to be directionally dependent. Diffusion direction can be characterized by fractional anisotropy (FA): an index of the tendency of water to diffuse in a single direction obtained by calculating a diffusion tensor for each voxel (i.e., diffusion tensor imaging or DTI). Proton diffusion in WM is typically parallel to fiber tracts; and therefore, FA and other DTI indices provide measures of WM integrity (Ringman et al., 2007) and may distinguish demyelinating from degenerative processes (Song et al., 2003). DTI can help delineate anatomical WM changes, but SP in *PSEN1*-related AD has not been well described electrophysiologically. Such characterization can help delineate the nature and extent of WM tract involvement.

Through the development of ligands that bind relatively selectively to fibrillar amyloid and can be radioactively labeled to allow detection using positron emission tomography ("amyloid PET"), we can now identify and localize amyloid deposition during life (Klunk et al., 2003). The relationship between the distribution of such pathology to defined anatomical pathways can help elucidate the role amyloid plaques play in symptom manifestation. In the present article, we sought to comprehensively assess the MRI characteristics of WM involvement in SP in 3 carriers of the A431E *PSEN1* mutation relative to 7 persons symptomatic from *PSEN1* mutations but without SP. Furthermore, we performed additional assessments with amyloid PET using Pittsburgh Compound B (PiB) and motor- and somatosensory-evoked potential studies in 1 A431E *PSEN1* mutation carrier with SP.

2. Methods

2.1. Subjects

Subjects or their surrogates gave written informed consent as part of an Institutional Review Board-approved observational study of ADAD at the University of California at Los Angeles. The 10 subjects that were included were symptomatic from known pathogenic *PSEN1* mutations, were aware of their mutation status, and had DTI available. Subjects underwent comprehensive clinical evaluations including the Mini-Mental Status Examination (Folstein et al., 1975) and Clinical Dementia Rating scale (Morris, 1997). The Clinical Dementia Rating (CDR) scale is a global scale of dementia severity based on an interview with the subject and a knowledgeable informant. A score of 0 represents normalcy, 0.5 indicates questionable or mild impairment, 1 mild, 2 moderate, and 3 severe dementia. The subjects were defined as having SP if leg spasticity interfered with their ability to ambulate before or within 2 years of the onset of cognitive symptoms. Time since onset of cognitive or motor symptoms was quantified in years. Subjects also underwent apolipoprotein E (*APOE*) genotyping using standard techniques.

2.2. Image acquisition

All subjects underwent structural T1-weighted MRI scans and DTI. All subjects but one (without SP) underwent susceptibility-weighted imaging (SWI) or T2-star weighted (T2*) MRIs from which microhemorrhage (MCH) count could be evaluated. Eight subjects underwent fluid attenuated inversion recovery (FLAIR) MRI sequences (3 with SP and 5 without), and 5 subjects had a PiB PET scan (1 with SP and 4 without).

All MR images were obtained on the same 3T Siemens Trio Scanner using a 32-channel phased array head-coil. The DTI protocol has been previously described (Ryan et al., 2013) and consisted of 64 gradient directions acquired via a single-shot spin-echo echo planar imaging sequence (field of view 240 mm, matrix 96×96, yielding an isotropic voxel of $2.5 \times 2.5 \times 2.5$ mm^3 and 55 contiguous axial slices, repetition time, TR = 6800 ms, echo time, TE = 91 ms, b-value = 1000 s/mm^2, augmented with parallel imaging acceleration [Generalized Autocalibrating Partially Parallel Acquisition; GRAPPA]). Nine acquisitions without diffusion weighting (b = 0 s/mm^2) were also acquired.

All subjects also underwent volumetric structural T1-weighted imaging using Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE), obtained in the sagittal plane (TR = 2300 ms, TE = 2.95 ms, voxel resolution=$1.1 \times 1.1 \times 1.2$ mm^3). To evaluate for the presence of MCHs, 6 subjects underwent SWI in the axial plane (TR = 28 ms, TE = 20 ms, voxel resolution=$0.7 \times 0.7 \times 2.4$ mm^3) and 3 underwent T2* in the axial plane (TR = 650 ms, TE = 20 ms, voxel resolution = $0.8 \times 0.8 \times 4$ mm^3). To evaluate for the presence and extent of white matter hyperintensities (WMHs), 8 subjects underwent axial T2-weighted FLAIR MRI imaging (TR = 9000 ms, TE = 90 ms, voxel resolution = $0.9 \times 0.9 \times 5.0$ mm^3).

Five subjects also underwent a PiB scan (1 with SP, "AJ", and 4 without). PiB imaging was performed with a bolus injection of approximately 15 mCi of [^{11}C]PiB. Dynamic acquisition consisted of either a 70-minute scan starting at injection or a 30-minute scan beginning 40 minutes after injection.

2.3. Image processing and analysis of DTI data

DTI processing was performed using the Diffusion-Weighted Imaging Toolbox in FSL (http://www.fmrib.ox.ac.uk/fsl/). Before processing, the 2 diffusion sequences were averaged and then concatenated with the 9 B0 acquisitions to create a single 4D volume for processing. For 1 subject without SP, only 1 DTI volume was acquired. Volumes were subjected to eddy current correction and linear realignment to the first image. Diffusion tensors were then calculated after applying a brain mask generated from FSL's Brain Extraction Tool. The resulting FA, MD, axial diffusivity, and radial diffusivity (RD) maps were used for analysis. Conversion of all outputs to standard space was achieved via FSL's Tract Based Spatial Statistics toolbox, which performed nonlinear registration to FSL's FA template map followed by a sequential nonlinear and affine transformation into Montreal Neurological Institute (MNI) space. The processed FA images were then combined to generate a mean FA image for the group, which was used to create a mean FA "skeleton" to limit voxel statistics to WM. A threshold of 0.20 was used to include WM tracts that were both common to all subjects and the most aligned, while excluding potential non-WM regions. Individual subject FA images were then projected onto this skeleton to create skeletonized FA images for statistical analysis.

2.4. Volumetric analyses

The MPRAGE images of all subjects were registered in the same space and automatically segmented to obtain cortical