ELSEVIER

Neurobiology of Aging 34 (2013) 636–639

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Brief communication

Frontal asymmetry in behavioral variant frontotemporal dementia: clinicoimaging and pathogenetic correlates

Jennifer L. Whitwell[a,*], Jia Xu[b], Jay Mandrekar[b], Bradley F. Boeve[c], David S. Knopman[c], Joseph E. Parisi[d], Matthew L. Senjem[e], Dennis W. Dickson[f], Ronald C. Petersen[c], Rosa Rademakers[g], Clifford R. Jack, Jr.[a], Keith A. Josephs[c]

[a] *Department of Radiology, Mayo Clinic, Rochester, MN, USA*
[b] *Department of Health Sciences Research (Biostatistics), Mayo Clinic, Rochester, MN, USA*
[c] *Department of Neurology, Mayo Clinic, Rochester, MN, USA*
[d] *Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA*
[e] *Department of Information Technology, Mayo Clinic, Rochester, MN, USA*
[f] *Department of Neuropathology, Mayo Clinic, Jacksonville, FL, USA*
[g] *Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA*

Received 4 January 2012; received in revised form 6 March 2012; accepted 15 March 2012

Abstract

We aimed to assess associations between clinical, imaging, pathologic, and genetic features and frontal lobe asymmetry in behavioral variant frontotemporal dementia (bvFTD). Volumes of the left and right dorsolateral, medial, and orbital frontal lobes were measured in 80 bvFTD subjects and subjects were classified into 3 groups according to the degree of asymmetry (asymmetric left, asymmetric right, symmetric) using cluster analysis. The majority of subjects were symmetric (65%), with 20% asymmetric left and 15% asymmetric right. There were no clinical differences across groups, although there was a trend for greater behavioral dyscontrol in right asymmetric compared with left asymmetric subjects. More widespread atrophy involving the parietal lobe was observed in the symmetric group. Genetic features differed across groups with symmetric frontal lobes associated with *C9ORF72* and tau mutations, while asymmetric frontal lobes were associated with progranulin mutations. These findings therefore suggest that neuroanatomical patterns of frontal lobe atrophy in bvFTD are influenced by specific gene mutations.

Keywords: Frontotemporal dementia; Frontal lobes; MRI; Asymmetry; Microtubule associated protein tau; Progranulin; *C9ORF72*; Pathology

1. Introduction

Behavioral variant frontotemporal dementia (bvFTD) is a progressive neurodegenerative disorder characterized by behavioral and personality change (Neary et al., 1998). It is often associated with atrophy of the frontal lobes, although neuroanatomical subtypes have been identified with differing patterns of frontal, temporal, and parietal involvement (Whitwell et al., 2009). Frontal atrophy is generally regarded as being symmetric, or right-side predominant (Boccardi et al., 2002), yet a systematic assessment of asymmetry in bvFTD is lacking. The aims of this study therefore were to determine whether clinical, neuroanatomic, pathologic, and genetic features differ between (1) subjects with asymmetric left versus asymmetric right frontal lobe atrophy, and (2) subjects with asymmetric frontal lobe atrophy (right or left) versus those with symmetric frontal lobe atrophy.

2. Methods

We identified 97 subjects from the Mayo Clinic Alzheimer's Disease Research Center (ADRC) with a clinical

* Corresponding author at: Department of Radiology, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905, USA. Tel.: +1-507-284-5576; fax: +1-507-284-9778.
E-mail address: whitwell.jennifer@mayo.edu (J.L. Whitwell).

0197-4580/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
10.1016/j.neurobiolaging.2012.03.009

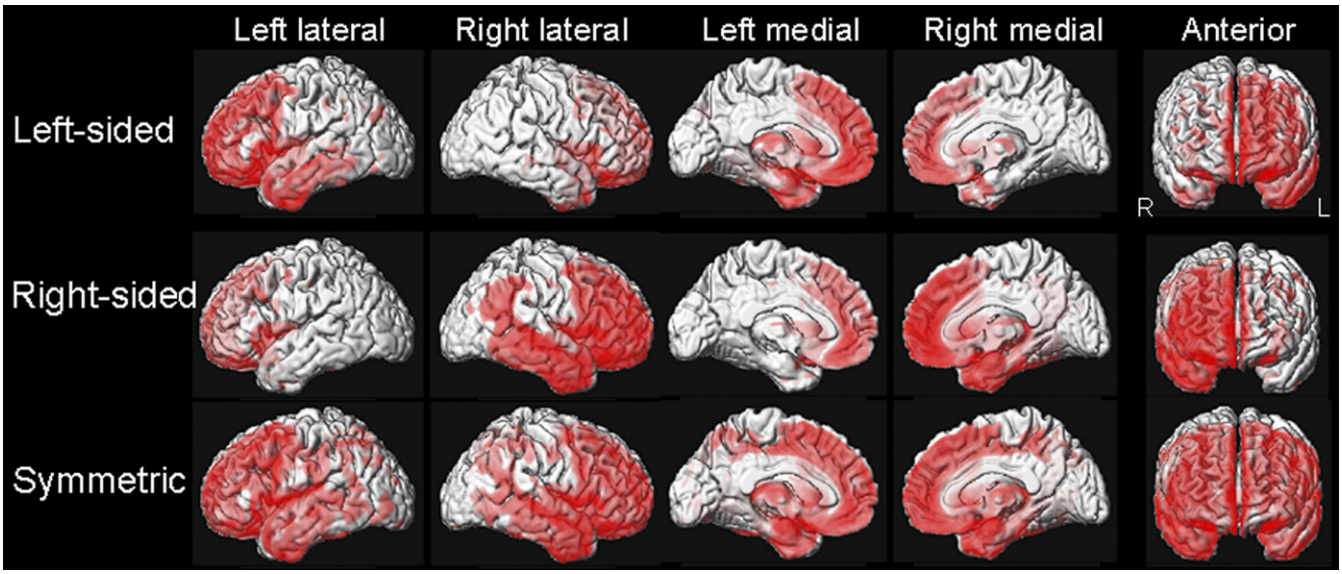

Fig. 1. Voxel-based morphometry patterns of gray matter loss in asymmetric left (left-sided), asymmetric right (right-sided) and symmetric behavioral variant frontotemporal dementia (bvFTD) versus controls (family-wise error corrected, $p < 0.05$).

diagnosis of bvFTD (Neary et al., 1998) and magnetic resonance imaging (MRI). These subjects were age- and gender-matched to 30 healthy controls (mean ± standard deviation age at MRI = 61.2 ± 12.3 years; 63% female; compared with 60.6 ± 11.8 years; 56% female in bvFTD cohort).

All subjects had a T1-weighted volumetric MRI performed with a standardized protocol (Whitwell et al., 2009). All images underwent correction for gradient nonlinearity and intensity nonuniformity. The first MRI after presentation was used in all cases. An atlas-based parcellation technique was employed using SPM5 (http://www.fil.ion.ucl.ac.uk/SPM) and the automated anatomic labeling atlas in order to generate gray matter volumes for left and right medial frontal, dorsolateral frontal, and orbitofrontal lobe (Whitwell et al., 2009). *Z* scores were calculated using total intracranial volume-corrected frontal lobe volumes for each bvFTD subject compared with controls. In order to ensure that all bvFTD subjects had atrophy of the frontal lobes, all cases with *Z* scores less than −1 ($n = 17$) were excluded from the study. For the remaining 80 cases, hierarchical cluster analysis using average linkage method was performed using 3 variables of interest (difference between the left and right *Z* scores for medial frontal, dorsolateral frontal, and orbitofrontal lobes) to classify subjects in an unbiased manner into groups according to the degree of frontal lobe asymmetry. Voxel-based morphometry (VBM) (Ashburner and Friston, 2000) using SPM5 was utilized to assess patterns of gray matter atrophy across clusters, using standard processing (Whitwell et al., 2009).

All subjects with a positive family history that had available DNA were screened for mutations in the microtubule-associated protein tau (*MAPT*) and progranulin (*GRN*) gene (Gass et al., 2006; Hutton et al., 1998). In addition, subjects were screened for the GGGGCC hexanucleotide repeat in *C9ORF72* (Dejesus-Hernandez et al., 2011; Renton et al., 2011). Neuropathologic examinations were performed according to standard protocol. All cases were reclassified based on recent consensus recommendations (Mackenzie et al., 2009).

3. Results

The cluster analysis divided the cohort into 3 groups: 20% were classified by greater frontal atrophy in the left hemisphere (asymmetric left), 15% by greater frontal atrophy in the right hemisphere (asymmetric right), and 65% by symmetric atrophy (Supplementary Table 1). VBM patterns of frontal atrophy matched the cluster classifications (Fig. 1). However, the proportion of anatomical subtypes differed between asymmetric (asymmetric right and left groups combined) and symmetric bvFTD ($p = 0.001$) (Table 1). The temporofrontoparietal subtype was most common in symmetric bvFTD, whereas frontotemporal and frontal dominant subtypes were most common in asymmetric bvFTD.

No demographic, clinical, or pathological differences were observed across groups (Table 1). There was a trend for higher scores on the brief questionnaire version of the Neuropsychiatric Inventory in asymmetric right compared with asymmetric left bvFTD ($p = 0.07$). There were striking differences across groups in genetic associations. The majority of subjects with *C9ORF72* mutations (10/11, 91%) and *MAPT* mutations (10/16, 63%) had symmetric frontal atrophy, while the majority of subjects with *GRN* mutations had asymmetric frontal atrophy (5/6, 83%). Of those *MAPT* and *GRN* subjects that were asymmetric, a right-sided pat-