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PATTERNS OF ATROPHY IN PATHOLOGICALLY CONFIRMED FTLD WITH AND WITHOUT MOTOR NEURON DEGENERATION

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Abstract

We used voxel-based morphometry to compare the patterns of brain atrophy in two variants of pathologically confirmed frontotemporal lobar degeneration (FTLD), FTLD with motor neuron disease (FTLD-MND) and FTLD with ubiquitin-only-immunoreactive neuronal changes (FTLD-U). Patterns of atrophy were distinct and different from each other. A localized pattern of frontal lobe atrophy was found in FTLD-MND with a more widespread pattern of atrophy affecting the frontal and temporal lobes in FTLD-U.

Keywords

dementia; motor neuron disease; MRI; ubiquitin; voxel-based morphometry

INTRODUCTION

The frontotemporal dementias are characterized clinically by behavioral changes and aphasia, and pathologically by frontotemporal lobar degeneration (FTLD). Pathological diagnosis accounting for FTLD is heterogenous, but can be divided into tau-positive and tau-negative FTLD. Frontotemporal lobar degeneration with ubiquitin-only-immunoreactive neuronal changes (FTLD-U) and FTLD with motor neuron disease (FTLD-MND) are two variants of tau-negative FTLD¹. Both FTLD-U and FTLD-MND are characterized by the presence of ubiquitin-positive, tau and alpha-synuclein-negative intraneuronal inclusions, leading some authorities to argue that these two entities may represent different points on the spectrum of a single disease.

A recent PET study demonstrated that patients with clinically defined frontotemporal dementia with MND show glucose hypometabolism only in the frontal cortex, while patients with frontotemporal dementia without MND had hypometabolism in both the frontal and temporal cortices². Since FTLD-U is the most common pathology underlying frontotemporal dementia³, we performed a voxel-based morphometry (VBM) analysis to investigate whether the patterns of atrophy on MRI in pathologically confirmed FTLD-U and FTLD-MND would correspond with these PET findings.

METHOD

Subjects

The Mayo Clinic database was used to identify all cases with a pathological diagnosis of FTLD-MND or FTLD-U and one volumetric MR scan. Of 57 cases of FTLD reviewed, 33 were pathologically confirmed to have FTLD-MND or FTLD-U, of which 18 had an MRI scan; eleven with FTLD-U and seven with FTLD-MND (table 1). All cases fulfilled consensus criteria for frontotemporal dementia⁴. For patients with more than one MRI scan, the first available in the series was used. There was no significant difference in age, gender, disease duration or Short Test of Mental Status score⁵ between the two groups; however the FTLD-MND group did have a shorter survival time ($p<0.001$). The cohort was age and gender-matched to a group of 18 healthy living controls.

Pathological analysis

Pathological methods were standard as previously described⁶, and diagnoses were made according to consensus criteria.^{1, 7}

FTLD-U was diagnosed if there was FTLD plus ubiquitin-positive, tau and alpha-synuclein negative, abnormal neurites or neuronal inclusions in frontotemporal cortex, or dentate granule cell layer, and an absence of histological evidence of motor neuron degeneration.

FTLD-MND was diagnosed if there was evidence of FTLD and lower motor neuron degeneration (loss of anterior horn cells in the spinal cord or hypoglossal motor neurons plus (1) shrunken residual motor neurons, (2) evidence of neuronophagia (3) Bunina bodies or ubiquitin-immunoreactive intraneuronal inclusions, either skein-like or hyaline-like), corticospinal tract degeneration (myelin and axonal loss and inflammatory cells in the absence of any vascular or other lesions than could account for this finding), or both. The term FTLD-MND represents pathological FTLD plus motor neuron degeneration, with clinical frontotemporal dementia. We included only one case of FTLD-MND with upper motor neuron disease only that fulfilled pathological criteria for FTLD-MND.^{1,7}

Image analysis

T1-weighted volumetric MRI scans were acquired at 1.5T (22×16.5cm FOV, 25° flip angle, 124 contiguous 1.6mm thick coronal slices). An optimized method of VBM was applied using both customized templates and prior probability maps⁸, implemented using SPM2 (<http://www.fil.ion.ucl.ac.uk/spm>). To create the customized template and priors all images were registered to the MNI template using a 12dof affine transformation and segmented into grey matter (GM), white matter (WM) and CSF using MNI priors. GM images were normalized to the MNI GM prior using a nonlinear discrete cosine transformation (DCT). The normalization parameters were applied to the original whole head and the images were segmented using the MNI priors. Average images were created of whole head, GM, WM and CSF, and smoothed using 8mm full-width at half-maximum (FWHM) smoothing kernel. All images were then registered to the customized whole brain template using a 12dof affine transformation and segmented using the customized priors. The GM images were normalized to the custom GM prior using a nonlinear DCT. The normalization parameters were then applied to the original whole head and the images were segmented once again using the customized priors. All images were modulated and smoothed with an 8mm FWHM smoothing kernel. Two-sided t-tests were used to compare the smoothed modulated images from the following groups: 1) FTLD-U v controls, 2) FTLD-MND v controls, 3) FTLD-U v FTLD-MND and 4) FTLD-MND v FTLD-U. Grey matter differences were assessed at an uncorrected statistical threshold ($p<0.001$), and after correction for multiple comparisons over the whole brain volume ($p<0.05$).

RESULTS

The FTLD-U group showed bilateral grey matter atrophy affecting both frontal and temporoparietal regions, compared to controls (uncorrected, $p < 0.001$, figure 1A and D). Regions of atrophy that survived the correction for multiple comparisons ($p < 0.05$) were found in the posterior temporal lobe, particularly the fusiform gyrus. In contrast, the FTLD-MND group showed bilateral grey matter atrophy largely restricted to the frontal lobes, with very little temporal lobe atrophy, compared to controls (uncorrected, $p < 0.001$, figure 1B and E); no regions survived the correction for multiple comparisons. The patterns of grey matter atrophy were symmetrical in both groups. On direct statistical comparison the FTLD-U group showed greater atrophy bilaterally in the posterior temporal lobe, specifically the superior temporal gyrus, than the FTLD-MND group (uncorrected, $p < 0.001$, figure 1C). No regions had greater atrophy in the FTLD-MND group than the FTLD-U group (uncorrected, $p < 0.001$).

DISCUSSION

This is the first volumetric MRI study to compare the patterns of atrophy in pathologically confirmed FTLD-U and FTLD-MND.

Voxel-based morphometry analysis revealed a predominantly frontal lobe pattern of atrophy in FTLD-MND, whereas in FTLD-U the pattern of atrophy was more widespread affecting the frontal, temporal and parietal lobes. This observation is similar to the patterns of hypometabolism reported in a recent PET study². However, in contrast we did not find significant hemispheric asymmetry in either group which may be due to the fact that our study utilized a pathologically confirmed cohort of two well defined variants and pathological diagnosis in clinically defined frontotemporal dementia is heterogeneous³. While these findings could suggest that FTLD-MND and FTLD-U are two different entities, an alternative explanation could be that the more widespread pattern of atrophy in FTLD-U is due to longer disease duration.

The pattern of atrophy in FTLD-MND was similar to the pattern of localized frontal lobe atrophy reported in ALS, a clinical subtype of MND⁹. The precentral gyrus was relatively spared in our cases of FTLD-MND where the atrophy was primarily premotor, extending back to the anterior precentral gyrus; an observation reported in a PET study on FTLD-MND², and an MRI study on ALS⁹.

Surprisingly, the most significant regions of atrophy in the FTLD-U group were found in the posterior temporal lobe. This differs from the traditional view that the anterior temporal lobe is the most severely affected temporal region in FTLD. In fact, this posterior temporal pattern is similar to that found in Alzheimer's disease, although lacks the characteristic involvement of the lateral and medial parietal lobes, especially the precuneus and posterior cingulate, seen in AD (figure 1D). This finding concurs with results of another VBM analysis from an independent pathologically confirmed series of FTLD-U, which also demonstrated posterior temporal lobe atrophy¹⁰. The reason for this pattern is unknown, but suggests that posterior temporal lobe atrophy may be a signature pattern of FTLD-U. A rigorous assessment of the sensitivity and specificity of this pattern for the purposes of clinical diagnosis could be useful, but requires a larger sample size.

This study suggests that in subjects with a clinical diagnosis of frontal variant frontotemporal dementia a symmetric pattern of atrophy restricted to the frontal lobes is suggestive of a pathological diagnosis of FTLD-MND, whereas a pattern of frontal and temporal lobe atrophy, with a posterior temporal predominance, suggests FTLD-U.

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Figure 1.

Surface rendering showing patterns of grey matter atrophy (shown in red) in A) FTLD-U compared to controls, B) FTLD-MND compared to controls, and C) FTLD-U compared to FTLD-MND (uncorrected, $p < 0.001$). In addition, the patterns of atrophy in FTLD-U and FTLD-MND compared to controls are displayed on a mid-slice render (D and E respectively); the brain has been split down the mid-sagittal plane using Analyze 6.1 and transparency renders through the left hemisphere (displayed on the right) and right hemisphere (displayed on the left) are shown.

Table 1

Patient characteristics

	FTLD-U (n=11)	FTLD-MND (n=7)	Controls (n=18)
Gender (M:F)	5:6	5:2	10:8
Age at scan (years)	62.5 ±10.5	52.2 ±13.8	58.8 ±12.6
Disease duration (onset-scan (years))	4.5 ± 2.5	2.3 ± 1.7	NA
Survival (onset-death (years))	8.9 ± 3.8	2.6 ± 2.0 *	NA
STM at scan	23.8 ± 8.8	23.6 ± 7.8	NA
Clinical evidence of motor neuron disease	0	5	NA
Pathological evidence of motor neuron degeneration (upper only)	0	7(1)	NA

Results are expressed as mean ± standard deviation; STM = Short test of mental status; NA = not applicable

* Significant difference between FTLD-U and FTLD-MND p<0.001 (t-test)