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Patterns of longitudinal brain atrophy in the logopenic variant of primary progressive aphasia

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ABSTRACT

The logopenic variant of primary progressive aphasia (PPA) is characterised by impaired sentence repetition and word retrieval difficulties. Post mortem studies, amyloid imaging and CSF tau/Aβ measurements suggest Alzheimer's disease (AD) pathology as the underlying cause. Relatively little is known about patterns of progression in patients with the logopenic variant of PPA. 21 patients (3 with post mortem confirmation of AD and 5 with positive amyloid PIB-PET scans) were studied with longitudinal T1-weighted MR imaging (mean interscan interval 1.2 years) using volumetric analysis and voxel-based morphometry (VBM). Baseline imaging showed asymmetrical (left greater than right) involvement of the posterior superior temporal and inferior parietal lobes as well as posterior cingulate and medial temporal lobes. The whole brain rate of volume loss was 2.0% per year with a greater rate of left hemisphere atrophy (2.3%/year) than right hemisphere (1.6%/year). Longitudinal VBM analysis showed increasing involvement of other areas in the left hemisphere (temporal, parietal, frontal and caudate) and atrophy of areas in the right hemisphere that had been involved earlier in the disease in the left hemisphere, particularly posterior cingulate/precuneus. With disease progression there was worsening of anomia, sentence repetition and sentence comprehension but consistent with the spread of imaging changes also deficits in single word comprehension, single word repetition and verbal memory. This study shows that the logopenic variant of PPA remains an asymmetrical disease, with spread through the left hemisphere language network but also involvement to a lesser degree of regions in the right hemisphere that mirror the earlier left hemisphere changes.

1. Introduction

The term primary progressive aphasia (PPA) refers to a group of neurodegenerative disorders with language dysfunction as their predominant symptom (Mesulam, 2001). Originally two subtypes, the semantic variant and the nonfluent/agrammatic variant, were described but more recently it has been recognised that there are further subtypes of PPA (Gorno-Tempini et al., 2004, 2008; Rohrer, Rossor, & Warren, 2010b). Recent consensus guidelines for diagnosis of PPA describe the features of a third subtype, the logopenic variant of PPA or lvPPA (Gorno-Tempini et al., 2011). This disorder has not been as well-studied as the others and unlike the semantic or nonfluent/agrammatic variants which are caused by frontotemporal lobar degeneration pathology (tau or TDP-43), lvPPA appears to be an atypical variant of Alzheimer's disease (AD), as evidenced by post-mortem studies (Mesulam et al., 2008; Rohrer, Rossor, & Warren, 2012b), positive amyloid PIB-PET imaging (Leyton et al., 2011; Rabinovici et al., 2008) and a high CSF tau/Aβ ratio (Rohrer et al., 2010a).

A number of cross-sectional imaging studies of lvPPA have now shown a consistent asymmetrical pattern of atrophy with particular emphasis on the areas around the left posterior middle/superior temporal lobe and inferior parietal lobe (temporo-parietal junction) but also the left posterior cingulate, precuneus and medial temporal lobe (Gorno-Tempini et al., 2004, 2008; Migliaccio et al., 2009; Rohrer et al., 2010a, 2012b; Wilson et al., 2010). However, few studies have examined longitudinal imaging in lvPPA (Knopman et al., 2009; Rogalski et al., 2011) and little is known about the patterns of change in atrophy over time.

This study aimed to look at longitudinal imaging patterns in lvPPA. We hypothesized (i) rates of whole brain and hemispheric atrophy would be similar to the other PPA subtypes; (ii) over time,

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there would be increasing involvement of more anterior areas in the left hemisphere; (iii) the contralateral hemisphere would become involved in a pattern similar to that seen first in the left hemisphere.

2. Methods

We identified all cases fulfilling consensus criteria for logopenic variant PPA (Gorno-Tempini et al., 2011) with at least two volumetric MRI scans of sufficient quality for analysis from the databases of the Dementia Research Centre at the University College London (UCL) Institute of Neurology and the Memory and Aging Center at the University of California, San Francisco (UCSF). In total, 21 patients were found (9 UCL and 12 UCSF) with three having post-mortem confirmation of Alzheimer's disease pathology and 5 having positive PIB-PET scans. All patients had undergone detailed clinical and neuropsychological assessment by an experienced behavioural neurologist and any available data on these patients were also extracted from the databases. Ethical approval for the study was obtained from the National Hospital for Neurology and Neurosurgery Local Research Ethics Committee and the UCSF Committee on Human Research.

Subjects were scanned on a 1.5T GE Signa (5), a 1.5T Siemens Magneton Vision (12) or a 3T Siemens Tim Trio (4). Initial image analysis was performed using the MIDAS software (Freeborough, Fox, & Kitney, 1997b). A rapid, semi-automated segmentation technique yielded a brain region separated from surrounding cerebrospinal fluid (CSF), skull and dura. Serial scans were aligned and volume change was calculated directly using the boundary shift integral (BSI) (Freeborough et al., 1997a). BSI-derived whole-brain volume changes (BBSI) were expressed as annualized volume change as a percentage of the baseline brain volume. For all patients and controls we also calculated left and right cerebral hemisphere volumes and rates of atrophy as well as left/right hemisphere volume ratios and rates of change of this hemispheric asymmetry ratio. Scans and associated brain regions were initially transformed into standard space by registration to the Montreal Neurological Institute (MNI) Template. Left and right hemispheric regions were defined using the MNI average brain which was split by dividing the whole volume along a plane coincident with the interhemispheric fissure. An intersection of each individual's brain region and the hemispheric regions defined on the MNI template was generated to provide measures of brain volume and atrophy in left and right hemispheres. Hemispheric atrophy was expressed as the difference in hemisphere volume between the repeat and baseline scans divided by the baseline hemisphere volume. Annualized rates of hemisphere atrophy were subsequently calculated by dividing by the interscan interval. Data from the lvPPA group were compared against a control group of 20 cognitively normal subjects by looking at the contrasts between the group means using a linear regression model in STATA12 (Stata Corporation, College Station, TX). Wilcoxon signed-rank test was used to look at within-disease group comparisons. There were no significant differences in age, gender, or interscan interval between the groups (Table 1).

To analyse regional patterns of atrophy cross-sectional voxel-based morphometry (VBM) was performed as previously described (Rohrer et al., 2010a) and detailed in the appendix. A control group of cognitively normal subjects matched for age and gender from both UCL (20) and UCSF (30) were included. We were also interested in assessing longitudinal patterns of change, for which we used a novel method for longitudinal VBM, described in the appendix. Voxel-based data were modelled with factors for group (controls or lvPPA patients, allowing unequal variance), gender (assuming equal variance), and scanner (eight levels, with equal variance assumed), and covariates for age and total intracranial volume (Barnes et al., 2010). For the longitudinal analysis, the logarithm of the interval between the scans was entered as an additional covariate.

Table 1
Mean (standard deviation) demographic and baseline volumetric MRI data.

	Controls	lvPPA
Number of subjects	20	21
Male:female ratio	12:8	12:9
Duration of disease (years)	N/A	4.6 (1.6)
Age at baseline scan (years)	63.8 (9.1)	64.4 (7.1)
Interscan interval (years)	1.7 (0.9)	1.2 (0.4)
Baseline brain volume (ml)	1180.6 (96.8)	1061.3 (100.8)*
Baseline left hemisphere volume (ml)	581.4 (45.4)	515.1 (49.6)*
Baseline right hemisphere volume (ml)	579.5 (47.8)	537.3 (48.7)*
Baseline left/right hemisphere ratio	1.00 (0.01)	0.96 (0.02)*

* $p < 0.05$ significant difference.

3. Results

3.1. Volumetric imaging

At baseline, brain and hemisphere volumes were significantly smaller in lvPPA than controls. Left hemisphere lobar volumes were significantly smaller than the right with a left/right hemisphere asymmetry ratio significantly lower than the control ratio (Table 1).

The rate of whole brain atrophy was significantly greater in lvPPA than controls at 2.0% per year versus 0.3% per year, $p < 0.05$ (Table 2, with individual atrophy rates shown in Fig. 1). Both left and right hemisphere rates of atrophy were greater than controls with the left hemisphere rate (2.3%) greater than the right hemisphere rate (1.6%) ($p = 0.003$). We subsequently went on to use standard methods to calculate sample sizes for detection of a moderate treatment effect (30% reduction in atrophy adjusting for control atrophy rate), including baseline and one follow-up assessment at 12 months with 90% power and 5% two-tailed significance level. For whole brain atrophy rate, the estimated sample size was 69, compared with 107 for the left hemisphere and 165 for the right hemisphere atrophy rate.

3.2. VBM analysis

Cross-sectional analysis revealed an asymmetrical pattern of grey matter atrophy in the lvPPA group compared with controls with a left-sided predominance (Fig. 2). The most significant areas of grey matter atrophy were in the left posterior temporal lobe (superior and middle temporal gyri), inferior parietal lobe and medial temporal lobe. However, the left posterior cingulate was also involved, as were the right parietal and temporal lobes (mostly posteriorly in the superior and middle temporal gyri and inferior parietal gyrus).

Table 2
Rates of whole brain and hemispheric atrophy and change in left/right hemisphere ratio.

Outcome measure	Mean rate of atrophy (standard deviation)	
	Controls	lvPPA
Brain BSI (%/year)	0.3 (0.4)	2.0 (0.9)*
Left hemisphere (%/year)	0.3 (0.9)	2.3 (1.8)*
Right hemisphere (%/year)	0.0 (0.9)	1.6 (1.4)*
L/R hemisphere ratio change (%/year)	0.3 (0.7)	0.8 (1.1)

* $p < 0.05$ significant difference, BSI = boundary shift integral.