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Clinical and neuroimaging biomarkers of amyloid-negative logopenic primary progressive aphasia

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ABSTRACT

Logopenic primary progressive aphasia (lvPPA) is a progressive language disorder characterized by anomia, difficulty repeating complex sentences, and phonological errors. The majority, although not all, lvPPA patients have underlying Alzheimer's disease. We aimed to determine whether clinical or neuroimaging features differ according to the deposition of Aβ on Pittsburgh-compound B PET in lvPPA. Clinical features, patterns of atrophy on MRI, hypometabolism on FDG-PET, and white matter tract degeneration were compared between six PiB-negative and 20 PiB-positive lvPPA patients. PiB-negative patients showed more asymmetric left-sided patterns of atrophy, hypometabolism and white matter tract degeneration, with greater left anteromedial temporal and medial prefrontal involvement, than PiB-positive patients. PiB-positive patients showed greater involvement of right temporoparietal and frontal lobes. There was very little evidence for clinical differences between the groups. Strikingly asymmetric neuroimaging findings with relatively preserved right hemisphere may provide clues that AD pathology is absent in lvPPA.

1. Introduction

The logopenic variant of primary progressive aphasia (lvPPA) is a progressive language disorder in which patients have anomia, difficulty retrieving words and repeating complex sentences and phonological errors in their spoken speech (Gorno-Tempini et al., 2011). These patients have preserved single word comprehension, grammar and syntax, and typically do not have apraxia of speech or dysarthria. On neuroimaging, patients with lvPPA typically show abnormalities in the temporoparietal cortex, with greater involvement of the left hemisphere (Gorno-Tempini et al., 2004; Madhavan et al., 2013; Rohrer, Ridgway, et al., 2010; Rogalski et al., 2011; Teichmann et al., 2013). Pathological studies, and studies that have utilized beta-amyloid (Aβ) imaging or CSF biomarkers, have shown that the majority of patients with lvPPA have underlying Alzheimer's disease (AD) (Leyton et al., 2011; Mesulam et al., 2008; Rabinovici et al., 2008; Teichmann et al., 2013). Hence, lvPPA is often considered an atypical clinical variant of AD (Whitwell et al., 2011). However, lvPPA patients have been reported that do not show Aβ deposition on imaging, suggesting a different underlying pathological etiology in these patients. It appears that in these instances lvPPA may arise from frontotemporal lobar degeneration (FTLD) pathology (Hu et al., 2010; Mesulam, Weintraub, et al., 2014; Mesulam et al., 2008), most commonly from FTLD characterized by the presence of the protein TDP-43, and may even be associated with FTLD-related genetic mutations, such as progranulin gene mutations (Hu et al., 2010; Josephs et al., 2014; Rohrer, Crutch, Warrington, & Warren, 2010). The proportion of lvPPA patients that do not have AD varies between 0% and 38% across studies (Chare et al., 2014; Hu et al., 2010; Leyton et al., 2011; Mesulam et al., 2008; Rabinovici et al., 2008; Teichmann et al., 2013).

It is unclear whether there are any clinical or neuroimaging differences between lvPPA patients that do or do not have underlying

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AD pathology, and hence whether it would be possible to determine which patients will not have AD. This will be critically important for patient care and prognosis, especially when treatments that can slow the AD neurodegenerative process become available. Predicting the underlying pathology would be particularly useful in non-tertiary care centers where amyloid imaging is not available. Previous studies utilizing autopsy-confirmed cohorts have suggested that neuroimaging can be useful to help predict underlying pathology, with specific signatures identified for AD and for FTLD across a number of clinical syndromes (Josephs et al., 2008, 2010; Lee et al., 2011; Lehmann et al., 2010; Rohrer, Geser, et al., 2010; Whitwell, Jack, Boeve, et al., 2010; Whitwell, Jack, Parisi, et al., 2010; Whitwell et al., 2011). It is unknown, however, whether neuroimaging features differ according to pathology within the lvPPA syndrome.

The aim of this study was therefore to investigate whether there are any clinical or neuroimaging differences between lvPPA patients that do and do not have Aβ deposition on Pittsburgh compound B (PiB) PET imaging, and to determine the degree to which these variables can differentiate the groups. The neuroimaging analysis included MRI, 18-F-fluorodeoxyglucose PET (FDG-PET) and diffusion tensor imaging (DTI), and we analyzed regions that have been particularly associated with AD pathology, FTLD pathology or the presence of progranulin mutations.

2. Material and methods

2.1. Subjects

A total of 50 patients with lvPPA were consecutively recruited from the Department of Neurology, Mayo Clinic between October 1st 2010 and July 1st 2013. All patients underwent a detailed neurological and speech and language assessment as detailed below. Clinical diagnosis was rendered based solely on data from speech and language assessments without any reference to neurological or neuroimaging results. All patients presented with deficits in language, with language being the dominant symptom and the primary cause for problems in activities of daily living. The diagnosis of lvPPA was independently determined by two speech-language pathologists (JRD and EAS) by consensus. Criteria for the diagnosis of lvPPA were compatible with published consensus criteria (Gorno-Tempini et al., 2011), and included: (1) presence of aphasia, (2) impaired sentence repetition and comprehension, (3) presence of anomia with evidence of spared single word comprehension, (4) evidence of phonemic paraphasias, (5) normal rate of verbal expression or slowed verbal expression due to pauses for word retrieval without evidence of motoric slowing or apraxia of speech, and (6) absence of agrammatic/telegraphic verbal output. All patients showed patterns of left posterior perisylvian or parietal atrophy and hypometabolism characteristic of lvPPA. No patients showed the imaging patterns characteristic for the semantic and agrammatic variants of PPA, as defined in the consensus criteria (Gorno-Tempini et al., 2011). All 50 patients qualitatively met published consensus criteria for lvPPA (Gorno-Tempini et al., 2011).

All patients underwent PiB-PET scanning and patients were classified as PiB-positive or PiB-negative using a global SUVR ratio cut-point of 1.5 that was generated using an automated analysis pipeline previously described in detail (Jack et al., 2008). Of the 50 lvPPA patients, six were classified as PiB-negative (12%) and 44 were classified as PiB-positive (88%). The PiB-PET scans for the six PiB-negative patients are shown in Supplemental Fig. 1, and a scatter-plot showing the global and regional SUVR values for each patient is shown in Supplemental Fig. 2. For this study, we compared the six PiB-negative patients to all PiB-positive patients that had a similar disease duration of three years or less ($n = 20$) to eliminate any potential biases that could have been caused by imbalances in disease duration.

2.2. Speech and language assessment

The speech and language battery was performed by one of two Speech-Language Pathologists (JRD or EAS). The battery included the Western Aphasia Battery (WAB), revised (Kertesz, 2007), Part 1, as a primary measure of global language ability. Specific subtest scores on the WAB were used to index information content, and fluency and grammatical adequacy and paraphasias, during narrative picture description; word and sentence repetition ability; and animal fluency. The 15-item Boston Naming Test (Lansing, Ivnik, Cullum, & Randolph, 1999) served as a sensitive measure of confrontation naming, the 22-item version of Part V of DeRenzi and Vignolo's Token Test (DeRenzi & Vignolo, 1962) served as a challenging measure of verbal comprehension ability (Wertz, Keith, & Custer, 1971), and the Pyramids and Palm Trees test (Howard & Patterson, 1992) served as a measure of object knowledge. Action (verb) (Piatt, Fields, Paolo, Koller, & Troster, 1999) fluency was also assessed. Phonological errors were rated on a four-point scale (absent, mild, moderate-marked, severe) during consensus review of recorded conversation as well as spoken picture description and word and sentence repetition responses during the formal test battery. The presence or absence of motor speech abnormalities were determined by the two speech-language pathologists (JRD and EAS).

2.3. Cognitive assessment

All patients underwent detailed neuropsychological assessments (Josephs et al., 2012) including the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975), Trail Making Test (TMT) A (Spreen & Strauss, 1998), the Delis-Kaplan Executive Function System Card Sort (DKEFS) (Delis, Kaplan, & Kramer, 2001), the Wechsler Memory Scale III (Wechsler, 1987); and the Visual Object and Space Perception Battery (VOSP) (Warrington & James, 1991). Mayo Older American Normative Studies age and education-adjusted scaled scores (Ivnik et al., 1992) were used for all neuropsychological variables except for the DKEFS Card Sort and VOSP Cube Analysis. The MOANS and DKEFS Card Sort are constructed to have a mean of 10 and standard deviation of 3 in cognitively healthy participants.

2.4. Genetic testing

All patients underwent apolipoprotein E (APOE) genotype testing, as previously described (Josephs, Tsuboi, Cookson, Watt, & Dickson, 2004), and were tested for the presence of progranulin, microtubule associated protein tau (MAPT) and TARDBP gene mutations and the expanded GGGGCC hexanucleotide repeat in C9ORF72, as previously described (Baker et al., 2006; Dejesus-Hernandez et al., 2011; Hutton et al., 1998; Rutherford et al., 2008).

2.5. Image acquisition

All patients underwent MRI, FDG-PET and PiB PET scanning within two days of the clinical evaluations. The MRI imaging protocol was performed on a 3T GE scanner, and included a 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence and a DTI sequence with 41 diffusion encoding steps and four non-diffusion (b0) weighted T2 images. All PET scans were acquired using a PET/CT scanner (GE Healthcare, Milwaukee, Wisconsin) operating in 3D mode. Detailed acquisition details have been previously published (Josephs et al., 2012).