Alzheimer's pathology in primary progressive aphasia

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Abstract

Primary progressive aphasia (PPA) is a neurodegenerative disorder with language impairment as the primary feature. Different subtypes have been described and the 3 best characterized are progressive nonfluent aphasia (PNFA), semantic dementia (SD) and logopenic/phonological aphasia (LPA). Of these subtypes, LPA is most commonly associated with Alzheimer's disease (AD) pathology. However, the features of PPA associated with AD have not been fully defined. Here we retrospectively identified 14 patients with PPA and either pathologically confirmed AD or cerebrospinal fluid (CSF) biomarkers consistent with AD. Analysis of neurological and neuropsychological features revealed that all patients had a syndrome of LPA with relatively nonfluent spontaneous speech, phonemic errors, and reduced digit span; most patients also had impaired verbal episodic memory. Analysis of the pattern of cortical thinning in these patients revealed left posterior superior temporal, inferior parietal, medial temporal, and posterior cingulate involvement and in patients with more severe disease, increasing involvement of left anterior temporal and frontal cortices and right hemisphere areas in the temporo-parietal junction, posterior cingulate, and medial temporal lobe. We propose that LPA may be a "unihemispheric" presentation of AD, and discuss this concept in relation to accumulating evidence concerning language dysfunction in AD.
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1. Introduction

Primary progressive aphasia (PPA) refers to a group of neurodegenerative disorders with language impairment as the initial symptom (Mesulam, 1982, 2001, 2003). These disorders are of high neurobiological and clinical importance because they illustrate the potentially focal nature of neurodegenerative disease and the potential heterogeneity of clinical presentations even where the underlying pathological process is uniform. The best characterized subtypes of PPA are progressive nonfluent aphasia (PNFA) and semantic dementia (SD). Patients with PNFA have nonfluent speech characterized by agrammatism and/or a motor speech impairment (usually an apraxia of speech, i.e., hesitancy and effortfulness attributable to impaired planning of articulation) (Ogar et al., 2007). SD presents with fluent aphasia, anomia, and single word comprehension deficits secondary to verbal semantic impairment (Hodges and Patterson, 2007). "Fluency" in this context refers to the flow of speech. However, dysfluency may arise from a variety of underlying deficits, including agrammatism, impaired articulation (motor deficits such as apraxia of speech), decreased phrase length or slower speech rate (e.g., due to word-finding pauses); patients referred to as having a "nonfluent aphasia" may have various more or less distinct primary language or speech impairments. This theme is well illustrated by the recently recognized entity of logopenic/phonological aphasia (LPA) (Gorno-Tempini et al., 2004, 2008), which constitutes a third major syndrome within the PPA spectrum. Patients with LPA have word-finding pauses and anomia as well as impaired speech repetition, particularly sentences (Gorno-Tempini et al., 2008).

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Most cases of PPA have a non-Alzheimer pathological substrate within the frontotemporal lobar degeneration spectrum, and are usually associated predominantly with either tau- or TAR (trans-activation-response) DNA binding protein 43 (TDP-43)-positive cellular inclusions (known as FTLD-tau or FTLD-TDP pathology), respectively (Knibb et al., 2006; Snowden et al., 2007). However, it has long been recognized that PPA syndromes may also be associated with Alzheimer's disease (AD) pathology (Clark et al., 2003; Green et al., 1990, 1996; Karbe et al., 1993; Kempler et al., 1990; Li et al., 2000; Pogacar and Williams, 1984) and in recent years more detailed series have been reported (Alladi et al., 2007; Croot et al., 2000; Davies et al., 2005; Galton et al., 2000; Josephs et al., 2008; Kertesz et al., 2005; Knibb et al., 2006; Mesulam et al., 2008). In particular, recent evidence has suggested that LPA is underpinned by AD pathology in a high proportion of cases and may be the most common aphasia phenotype of AD (Gorno-Tempini et al., 2008; Mesulam et al., 2008; Rabinovici et al., 2008). However both PNFA and SD have also been reported with AD pathology, as have syndromes that do not fit clearly into a single category, so-called "mixed" aphasia (Alladi et al., 2007; Knibb et al., 2006). As AD is the most common neurodegenerative disease of later life, the range of phenotypic variation in AD and the mechanisms that drive this variation are key issues in the field of neurodegenerative disease.

Here we review the clinical, neuropsychological and cross-sectional neuroimaging features of a retrospective series of patients with a clinical diagnosis of PPA and AD pathology either demonstrated directly or presumed on the basis of cerebrospinal fluid (CSF) biomarker profiles. We consider these cases in relation to previously published series of PPA patients with either pathologically confirmed AD or a positive Pittsburgh compound B (PIB)-positron emission tomography (PET) scan suggestive of AD.

2. Methods

From the Dementia Research Centre patient database comprising a consecutive series of patients seen between 1992 and 2008, we extracted all cases meeting criteria for PPA (Mesulam, 2001, 2003) and who had either AD pathology at postmortem/cerebral biopsy or CSF biomarker data consistent with Alzheimer pathology (raised CSF total tau level with reduced amyloid Aβ42 fraction; Blennow and Hampel, 2003; Hulstaert et al., 1999; Tapiola et al., 2009). In total, 14 patients were included in the series: 9 had pathologically confirmed Alzheimer's disease (7 who came to postmortem and 2 on cerebral biopsy) and 5 had CSF biomarkers consistent with AD (these 5 patients were previously reported in Rohrer et al., 2010). Clinical notes and neuropsychological data were reviewed, and the clinical diagnosis at the time the patient was initially assessed and a revised clinical diagnosis based on current descriptive criteria for PPA (Mesulam, 2001, 2003; Gorno-Tempini et al., 2004, 2008) were recorded in each case. Neuropsychological data were also recorded where available. Ethical approval for the study was obtained from the National Hospital for Neurology and Neurosurgery Local Research Ethics Committee. Written research consent was obtained from all patients participating in the study.

2.1. Brain imaging analysis

All subjects had been scanned on a 1.5 T GE Signa unit scanner (General Electric, Milwaukee, WI) with T1-weighted volumetric images obtained with a 24-cm field of view and 256 × 256 matrix to provide 124 contiguous 1.5-mm-thick slices in the coronal plane. Mean (standard deviation) age at scan was 60.2 (6.2) years. A control group of 23 age- and gender-matched cognitively normal subjects (mean age 63.5 [7.3] years at time of scan) was used for comparison. No subject had significant cerebrovascular disease or other secondary pathology on neuroimaging. Image analysis was performed using the MIDAS software package (Freeborough et al., 1997). A rapid, semiautomated technique of brain segmentation which involves interactive selection of thresholds, followed by a series of erosions and dilations was performed for each scan. This yielded a brain region which was separated from surrounding CSF, skull, and dura giving a baseline brain volume. Ventricles were also segmented within MIDAS. Scans and associated brain regions were initially transformed into standard space by registration to the Montreal Neurological Institute (MNI) Template (Mazziotta et al., 1995). Left and right hemispheric regions were defined using the MNI average brain which was split by dividing the whole volume along a line 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 a measure of brain volume in left and right hemispheres and left/right volume ratios were also calculated. The 2 disease groups and the healthy control group were compared statistically based on contrasts between the group means using a linear regression model in STATA10 (Stata Corporation, College Station, TX).

We investigated changes in imaging patterns with severity using cortical reconstruction and thickness estimation methods with the Freesurfer image analysis suite (surfer.nmr.mgh.harvard.edu/) as previously described (Rohrer et al., 2009). We used performance on the Graded Naming Test (McKenna and Warrington, 1980, total number of items equals 30) (i.e., degree of anomia) as a measure of disease severity, splitting the group according to their score: group 1 (less severe: 9 patients) scored > 0 (mean 7.7, standard deviation 9.2) and group 2 (more severe: 4 patients) were unable to score. One case (AD-PPA6) with greater right than left hemisphere atrophy was not included in this analysis; this atrophy profile might reflect either a different disease phenotype or reversed hemisphere lan-