



Identification of an atypical variant of logopenic progressive aphasia



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ARTICLE INFO

Article history:

Available online 6 April 2013

Keywords:

Primary progressive aphasia
Logopenic aphasia
Neurocognitive impairment
Temporoparietal atrophy
Voxel-based morphometry

ABSTRACT

The purpose of this study was to examine the association between aphasia severity and neurocognitive function, disease duration and temporoparietal atrophy in 21 individuals with the logopenic variant of primary progressive aphasia (lvPPA). We found significant correlations between aphasia severity and degree of neurocognitive impairment as well as temporoparietal atrophy; but not disease duration. Cluster analysis identified three variants of lvPPA: (1) subjects with mild aphasia and short disease duration (mild typical lvPPA); (2) subjects with mild aphasia and long disease duration (mild atypical lvPPA); and, (3) subjects with severe aphasia and relatively long disease duration (severe typical lvPPA). All three variants showed temporoparietal atrophy, with the mild atypical group showing the least atrophy despite the longest disease duration. The mild atypical group also showed mild neuropsychological impairment. The subjects with mild aphasia and neuropsychological impairment despite long disease duration may represent a slowly progressive variant of lvPPA.

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1. Introduction

The logopenic variant of primary progressive aphasia (lvPPA) is a clinical phenotype distinct from other types of language impairment that occur secondary to neurodegeneration, (i.e., agrammatic PPA and the semantic variant of PPA) (Gorno-Tempini et al., 2008, 2011) and other variants of Alzheimer's disease (early-onset typical amnesic AD and posterior cortical atrophy) (Migliaccio et al., 2009; Ridgway et al., 2012). Characteristic features of lvPPA include impaired word retrieval in spontaneous speech and naming, impaired repetition of sentences and phrases, phonologic errors in spontaneous speech, and relatively spared single word comprehension, object knowledge and motor speech (Gorno-Tempini et al., 2011).

Imaging studies of lvPPA consistently show a pattern of gray matter reduction and cortical thinning affecting primarily the left temporoparietal cortex, including the inferior parietal lobe, posterior middle and superior temporal gyri, and Brodmann area 37 which is evident at early stages of the disease process (Gorno-Tempini et al., 2004, 2008; Mesulam, Wieneke, Thompson, Rogalski, & Weintraub, 2012; Mesulam et al., 2009; Migliaccio et al., 2009;

Ridgway et al., 2012; Rohrer et al., 2010; Sapolsky et al., 2010). A longitudinal study showed that as the disease progresses, there also may be varying degrees of involvement of medial parietal and temporal lobes, posterior cingulate, right temporoparietal cortex and frontal regions (Rogalski et al., 2011).

Research shows that there is an association between regions of atrophy and degree of impairment in specific language functions in individuals with PPA. For example, one study found that naming correlated with bilateral temporal lobes, sentence repetition correlated with left superior temporal volumes, sentence comprehension correlated with left dorsal middle and inferior frontal gyri, and fluency correlated with left ventral middle and inferior frontal gyri (Amici et al., 2007). Another study also found an association between left inferior frontal cortical thickness and severity of impairment on fluency. Impairment in grammar/syntax also correlated with atrophy in this region. Unlike the previous study, severity of impairment in comprehension was correlated with left temporopolar cortical thickness (Sapolsky et al., 2010). A more recent longitudinal study of a group of subjects with PPA failed to find an association between percent change in total normalized cortical volume and percent change in the WAB-AQ over a two year period (Rogalski et al., 2011). Each of these studies evaluated the variants of PPA in aggregate (i.e., agrammatic, semantic, and logopenic variants were not separated out), and therefore the relationship between aphasia severity and gray matter changes unique to lvPPA is still unknown.

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Many studies of lvPPA include the assessment of neuropsychological function in addition to careful characterization of language deficits. Verbally mediated tasks, especially verbal memory and tasks that tap verbal working memory, such as digit and letter span, are commonly impaired relative to normal controls (Galantucci et al., 2011; Gorno-Tempini et al., 2004, 2008; Rabinovici et al., 2008; Rohrer et al., 2010; Wicklund, Rademaker, Johnson, Weitner, & Weintraub, 2007). Both cognitive and language data suggest a core deficit in phonologic loop functions (Gorno-Tempini et al., 2008). There also are varying degrees of impairment reported in other cognitive domains such as scanning and visuomotor tracking, divided attention and cognitive flexibility (i.e., regular and modified trailmaking test), and visuospatial/visuoconstructional abilities (i.e., VOSP Cube, regular and modified Rey-O Complex Figure) (Galantucci et al., 2011; Gorno-Tempini et al., 2004; Machulda et al., 2012; Rabinovici et al., 2008; Rohrer et al., 2010; Wicklund et al., 2007; Wilson et al., 2010). Although these studies provide information on cognitive dysfunction in lvPPA, none of them specifically examine the association between aphasia severity and degree of neurocognitive impairment.

As with other neurodegenerative conditions such as Alzheimer's Disease and frontotemporal dementia, individuals with PPA show a decline in cognitive function over time (Wicklund et al., 2007). Over an approximate three year period, the PPA subjects (which included agrammatic, semantic and logopenic variants) showed prominent decline on language measures. Attention and verbal memory also declined though the authors clarify that the decline in verbal memory was likely influenced by the aphasia (i.e., word access problems) rather than being representative of a true deficit in retention. No studies have specifically examined whether aphasia severity correlates with disease duration in PPA, and more specifically, in lvPPA.

It remains unclear how well neuropsychological function beyond the verbal domain and neuroimaging abnormalities correlate with aphasia severity and whether they represent good biomarkers of disease progression unique to lvPPA. In addition, it is unknown whether aphasia severity correlates well with disease duration. Understanding the relationships between the clinical features of lvPPA is important for determining patient prognosis; therefore, the aim of this study was to examine the association between aphasia severity and neurocognitive function, disease duration and temporoparietal atrophy in a group of well characterized individuals with lvPPA. Because disease duration did not correlate with aphasia severity in the patients studied, we also performed a cluster analysis to determine whether there were groups of outliers that would explain this lack of correlation.

2. Methods

2.1. Subjects

We recruited 21 subjects that met our clinical criteria for lvPPA. We included only subjects who spoke English as their primary language, and who had an informant to provide an independent evaluation of functioning [and corroboration of the history of language impairment].

All subjects underwent a detailed speech and language examination, neurological evaluation, neuropsychological testing and neuroimaging over a span of 48–72 h. All subjects had video and audio recordings of their entire formal speech and language assessment, as well as general conversation. Two speech-language pathologists (JRD and EAS) made the diagnosis of lvPPA prior to or during a consensus meeting, solely based on data from the speech and language assessment, without any knowledge of neurological, neuropsychological or neuroimaging results. The clinical

criteria used to determine a diagnosis for lvPPA were as follows: (1) presence of aphasia, (2) impaired sentence repetition and comprehension, (3) presence of anomia with evidence of relatively spared single word comprehension, (4) evidence of phonemic paraphasias, (5) slowed rate of verbal expression due to pauses for word retrieval or verbal formulation, and (6) absence of agrammatic or telegraphic verbal output. All subjects would also meet recent clinical consensus criteria for lvPPA (Gorno-Tempini et al., 2011).

Speech and language assessments included the Western Aphasia Battery (WAB), revised (Kertesz, 2007), Part A, as the primary measure of global language ability and aphasia severity, including the composite scores for Spontaneous Speech, Auditory Verbal Comprehension, Repetition, and Naming/Word Finding. The WAB aphasia quotient (AQ) was felt to be the best measure of disease severity given its comprehensive nature. All neurological assessments were performed by one Behavioral Neurologist (KAJ) and included the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) to assess global cognitive impairment, and the Clinical Dementia Rating Scale sum of boxes (CDR-SB) (Morris, 1993) to assess functional impairment.

Subjects also underwent neuropsychological assessments. A trained psychometrist administered all neuropsychological tests. A clinical neuropsychologist (MMM) oversaw test administration, scoring accuracy and quality control. The cognitive domains assessed (in addition to the comprehensive speech and language evaluation) included (1) memory [Wechsler Memory Scale-III (WMS-III) Logical Memory I/II which assesses immediate and delayed recall of paragraph-length stories and Visual Reproduction I/II which assesses immediate and delayed recall of designs (Wechsler, 1997) and Rey Auditory Verbal Learning Test (AVLT) (Rey, 1964) which is a list learning test that includes five learning trials, an interference trial, immediate recall and delay recall trials, and recognition]; (2) executive function [Trailmaking Test B (Reitan, 1958) which is a test of scanning and visuomotor tracking, divided attention, and cognitive flexibility and Delis-Kaplan Executive Function (DKEFS) Card Sort (Delis, Kaplan, & Kramer, 2001) which is a conceptual task that evaluates problem-solving, verbal and nonverbal concept formation, and flexibility of thinking]; and, (3) visuospatial function [Rey-Osterrieth Complex Figure Test (Osterrieth, 1944) which is a measure of visual perception and constructional praxis and Visual Object and Space Perception (VOSP) cube and incomplete letters subtests (Warrington & James, 1991). The VOSP cube subtest is a block counting task. The VOSP incomplete letter subtest shows a series of large alphabet letters, one to a card, which have been randomly degraded so that only 30% of the original shape remains. The subject is asked to identify the letter.]

Published norms were used for the WMS-III (Wechsler, 1997), VOSP (Bonello, Rapport, & Millis, 1997; Warrington & James, 1991), and DKEFS (Delis et al., 2001) subtests. Mayo Older American Normative Studies age-adjusted scaled scores were used for the AVLT, Trailmaking Test, and Rey-Osterrieth Complex Figure Test (Ivnik, Malec, Smith, Tangalos, & Petersen, 1996; Ivnik et al., 1992; Machulda et al., 2007). We converted age-adjusted scaled scores to z-scores for the WMS-III, AVLT, Trailmaking Test, DKEFS Card Sort, and Rey-Osterrieth Complex Figure Test. We calculated z-scores for VOSP performances based on published norms. Domain z-scores were calculated by averaging the z-scores for each test within a domain. A global z-score was calculated by averaging the z-scores for all three cognitive domains.

2.1.1. Standard protocol approvals and patient consents

The Mayo Clinic Institutional Review Board approved this study. All subjects provided written informed consent before participating in any research activity.

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