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Short communication

Quantitative assessment of grammar in amyloid-negative logopenic aphasia

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ABSTRACT

Logopenic primary progressive aphasia (lvPPA) typically results from underlying Alzheimer's disease, but subjects have been reported that do not show beta-amyloid (Aβ) deposition. These subjects do not differ on neurological and speech-language testing from Aβ-positive lvPPA, but they impressionistically show increased grammatical deficits. We performed a quantitative linguistic analysis of grammatical characteristics in Aβ-negative lvPPA compared to Aβ-positive lvPPA and agrammatic PPA, which is characterized by increased grammatical difficulties. Aβ-negative lvPPA used fewer function words and correct verbs but more syntactic and semantic errors compared to Aβ-positive lvPPA. These measures did not differ between Aβ-negative lvPPA and agPPA. Both lvPPA cohorts showed a higher mean length of utterance, more complex sentences, and fewer nouns than agPPA. Aβ-negative lvPPA subjects appear unique and share linguistic features with both agPPA and Aβ-positive lvPPA. Quantitative language analysis in lvPPA may be able to distinguish those with and without Aβ deposition.

1. Introduction

Logopenic primary progressive aphasia (lvPPA) is a neurodegenerative language disorder that typically presents with language difficulties, including impaired single-word retrieval, difficulties repeating sentences, and phonological errors, which are believed to be caused by an impairment in the phonological loop of the verbal working memory (Gorno-Tempini et al., 2008, 2011; Henry & Gorno-Tempini, 2010; Whitwell, Duffy, et al., 2015).

These language difficulties differ from those found in agrammatic PPA (agPPA), which is characterized by agrammatic and telegraphic language production and grammatical simplification; more specifically, these language impairments include deficits with the production of inflectional morphology, lower proportion or complete omission of function words, higher proportion of nouns compared to other open class words, use of nonfinite (untensed) verb forms, syntactic argument structure errors, and overall reduced sentence and grammatical complexity (Ash et al., 2009; Avrutin, 2001; Grossman et al., 1996; Thompson, Ballard, Tait, Weintraub, & Mesulam, 1997; Thompson et al., 2012; Wilson et al., 2010).

The majority of patients who are diagnosed with lvPPA have underlying Alzheimer's disease (AD) pathology, showing beta-amyloid (Aβ) and tau deposition on PET imaging (Mesulam et al., 2008; Rabinovici et al., 2008; Whitwell, Jones, et al., 2015). Because of this, lvPPA is often considered an atypical AD variant. However, some patients do not show Aβ deposition on PET scanning and are thus believed to have underlying frontotemporal lobar degeneration, likely with TDP-43 pathology, (Josephs et al., 2014; Matías-Guiu et al., 2015; Mesulam et al., 2014; Santos-Santos et al., 2018; Spinelli et al., 2017; Whitwell, Jones, et al., 2015).

Imaging differences have been reported between lvPPA patients who differ in the presence versus absence of Aβ deposition: Aβ-positive lvPPA show increased grey matter atrophy in the right hemisphere, while the volume loss in Aβ-negative lvPPA is more localized in the left temporal region (Whitwell, Duffy, et al., 2015). Despite these structural differences, very few differences exist between lvPPA subjects who are Aβ-positive versus those who are Aβ-negative on neurological and speech-language testing (Whitwell, Jones, et al., 2015). However, a previous case report observed grammatical deficits in one Aβ-negative lvPPA patient that were uncharacteristic of typical lvPPA language difficulties (Rohrer, Crutch, Warrington, & Warren, 2010). To further investigate this finding of different language impairments in Aβ-

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negative lvPPA, we performed a quantitative analysis of the grammatical characteristics of Aβ-negative lvPPA subjects to determine whether their linguistic properties differ from those of Aβ-positive lvPPA subjects and those of agrammatic PPA (agPPA) subjects, who characteristically have grammatical difficulties.

A cohort of 50 lvPPA subjects underwent neurological and speech-language assessments, as well as Pittsburgh Compound B (PiB) PET imaging to assess Aβ deposition. Six of these subjects were classified as Aβ-negative, as previously described (Whitwell, Jones, et al., 2015). The neurological, speech-language, genetic, and imaging findings have been previously reported for these six subjects (Josephs et al., 2014; Whitwell, Jones, et al., 2015). These six subjects were compared to 15 Aβ-positive lvPPA and 15 agPPA participants, who were matched by age, gender, and Western Aphasia Battery Aphasia Quotient (WAB-AQ) score (Kertesz, 2007). The picture description task of the WAB was video recorded, and these speech samples were transcribed and coded for quantitative comparison between groups for syntactic structures and errors that have been shown to reveal agrammatic deficits; these included coding all grammatical categories, as well as semantic and syntactic errors, among other language variables (Ash et al., 2010; Tetzloff et al., 2018; Thompson & Mack, 2014). By quantifying their language production in this manner, we were able to compare the grammatical deficits of Aβ-negative lvPPA to their Aβ-positive lvPPA counterparts, as well as agPPA subjects who are known to have syntactic deficits. We also assessed the patterns of grey matter atrophy in the Aβ-negative lvPPA, Aβ-positive lvPPA and agPPA subjects compared to controls to help us understand underlying neuroanatomical abnormalities.

2. Results

The three groups did not differ significantly in terms of age, gender, disease duration, education or WAB-AQ score (Table 1). No differences were observed between Aβ-negative and Aβ-positive lvPPA in neurological testing. The Aβ-negative group performed worse than agPPA on tests of verbal memory measured using the Auditory Verbal Learning Test, but did not differ from the Aβ-positive lvPPA group. However, all three groups performed comparably on testing of visual memory (Wechsler memory scale visual reproduction). The two lvPPA groups performed similarly on speech language testing, with Aβ-negative lvPPA showing worse sentence repetition than agPPA. Both lvPPA groups showed less Parkinsonism and apraxia of speech than the agPPA subjects. The neurological, neuropsychological and speech/language results of each individual Aβ-negative lvPPA subject have been previously published (Josephs et al., 2014).

Upon analyzing the speech samples, Aβ-negative lvPPA used a smaller proportion of verbs and function words (e.g., determiners, prepositions, etc.), had significantly fewer verbs that were produced with correct morphology, showed fewer utterances that were grammatical and more utterances that lacked a finite (tensed) verb form, and produced more syntactic and semantic errors than Aβ-positive lvPPA subjects (Table 2). These measures did not differ between AB-negative lvPPA and agPPA.

Both Aβ-negative and Aβ-positive lvPPA subjects showed a higher mean length of utterance (MLU), a greater proportion of complex utterances, and a smaller proportion of nouns than agPPA subjects (Table 2). Sample transcriptions from each participant group can be found in the Supplementary Material. Additionally, the grammatical results of each individual Aβ-negative lvPPA subject are shown in Table 3.

Both lvPPA groups showed grey matter loss in the temporoparietal lobes compared to controls, although the Aβ-negative subjects showed loss restricted to the left hemisphere and predominantly involved anterior regions of the temporal lobes (Fig. 1). The agPPA group showed grey matter loss bilaterally in the frontal lobes, although with greater involvement of the left hemisphere, and particularly targeted inferior frontal and medial frontal regions, with some additional loss observed in the left temporoparietal lobe. The Aβ-negative lvPPA group did not differ from the other groups after correction for multiple comparisons. However, when assessed uncorrected at $p < 0.001$, they showed smaller volumes in left anterior temporal lobe, but greater volumes in bilateral frontal regions, including the inferior frontal gyrus, compared to agPPA, and greater volumes in scattered regions in the right hemisphere compared to Aβ-positive lvPPA.

3. Discussion

Despite a common diagnosis of aphasia, the presence versus absence of Aβ deposition may influence the speech characteristics of lvPPA. In our original description, Aβ-negative lvPPA subjects were not clinically judged to have agrammatism, because their speech output was not what is typically observed in agPPA (e.g., function word omission, subject-object reversal) (Josephs et al., 2014). However, the present quantitative language analysis revealed inadequacies in these subjects that their Aβ-positive lvPPA counterparts lacked. These included reduced production of function words and correct verbs, more syntactic and semantic errors, and a greater proportion of non-utterances. Aβ-negative lvPPA did not differ from agPPA on these measures. However, both lvPPA groups produced longer utterances, lower proportion of nouns, and more syntactically complex utterances than agPPA, demonstrating better overall syntactic performance in lvPPA, regardless of Aβ status. Aβ-negative lvPPA subjects, therefore, appear to have a unique linguistic profile, sharing grammatical features with both agPPA and lvPPA.

On neuroimaging, the patterns of grey matter loss in the Aβ-negative lvPPA group were more typical of lvPPA, with both lvPPA groups showing predominant involvement of the temporoparietal lobes; likely underpinning their deficits in naming and sentence repetition. The agPPA group showed more striking involvement of the frontal lobe, particularly the inferior frontal gyrus, as others have previously found (Botha et al., 2015; Gorno-Tempini et al., 2004; Josephs et al., 2006; Mesulam et al., 2008). The fact that damage to Broca's area was not observed in Aβ-negative lvPPA, as previously shown in detail (Whitwell, Jones, et al., 2015), could support a view that the linguistic abnormalities observed in this cohort are fundamentally different, with a different underlying etiology, to those observed in agPPA. It is possible that areas of the language network, aside from Broca's area, may be responsible for the linguistic abnormalities observed in Aβ-negative lvPPA (Grossman et al., 2013). Sentence production is indeed supported not only by Broca's area but also regions in the temporal and parietal lobes. A functional MRI study that assessed brain regions involved in a picture description task showed that missing verbs, reduced sentence complexity and omission of function words were associated with changes in activation of the left posterior middle temporal gyrus and inferior parietal lobe, with the inferior frontal gyrus also involved in omission of function words (Schonberger et al., 2014). One structural difference between the lvPPA groups was that the Aβ-negative lvPPA subjects have significantly more grey matter atrophy in the left hemisphere than the right hemisphere, whereas Aβ-positive lvPPA show more bilateral patterns of degeneration (Whitwell, Duffy, et al., 2015). It is, therefore, possible that asymmetry of temporoparietal neurodegeneration could play a role in syntactic performance in Aβ-negative subjects.

Additionally, we previously showed that Aβ-negative lvPPA shows more hypometabolism on [^{18}F]fluorodeoxyglucose PET in anteromedial temporal regions compared to Aβ-positive lvPPA (Whitwell, Jones, et al., 2015). This could further explain the higher proportion of semantic errors and the general decreased syntactic performance in Aβ-negative subjects, as these regions compose part of the language network (Papathanassiou et al., 2000; Stowe, Haverkort, & Zwarts, 2005).

The implications of our findings to the diagnostic classification of our subjects deserve some discussion, as the presence of agrammatism