Clinical and MRI models predicting amyloid deposition in progressive aphasia and apraxia of speech

Jennifer L. Whitwell[a,*], Stephen D. Weigand[b], Joseph R. Duffy[c], Edythe A. Strand[c], Mary M. Machulda[d], Matthew L. Senjem[e], Jeffrey L. Gunter[e], Val J. Lowe[a], Clifford R. Jack Jr.[a], Keith A. Josephs[c]

[a]Department of Radiology, Mayo Clinic, Rochester, MN, USA
[b]Department of Health Sciences Research (Biostatistics), Mayo Clinic, Rochester, MN, USA
[c]Department of Neurology, Mayo Clinic, Rochester, MN, USA
[d]Department of Psychiatry and Psychology (Neuropsychology), Mayo Clinic, Rochester, MN, USA
[e]Department of Information Technology, Mayo Clinic, Rochester, MN, USA

ARTICLE INFO

ABSTRACT

Beta-amyloid (Aβ) deposition can be observed in primary progressive aphasia (PPA) and progressive apraxia of speech (PAOS). While it is typically associated with logopenic PPA, there are exceptions that make predicting Aβ status challenging based on clinical diagnosis alone. We aimed to determine whether MRI regional volumes or clinical data could help predict Aβ deposition. One hundred and thirty-nine PPA (n = 97; 15 agrammatic, 53 logopenic, 13 semantic and 16 unclassified) and PAOS (n = 42) subjects were prospectively recruited into a cross-sectional study and underwent speech/language assessments, 3.0 T MRI and C11-Pittsburgh Compound B PET. The presence of Aβ was determined using a 1.5 SUVR cut-point. Atlas-based parcellation was used to calculate gray matter volumes of 42 regions-of-interest across the brain. Penalized binary logistic regression was utilized to determine what combination of MRI regions, and what combination of speech and language tests, best predicts Aβ (+) status. The optimal MRI model and optimal clinical model both performed comparably in their ability to accurately classify subjects according to Aβ status. MRI accurately classified 81% of subjects using 14 regions. Small left superior temporal and inferior parietal volumes and large left Broca's area volumes were particularly predictive of Aβ (+) status. Clinical scores accurately classified 83% of subjects using 12 tests. Phonological errors and repetition deficits, and absence of agrammatism and motor speech deficits were particularly predictive of Aβ (+) status. In comparison, clinical diagnosis was able to accurately classify 89% of subjects. However, the MRI model performed well in predicting Aβ deposition in unclassified PPA. Clinical diagnosis provides optimum prediction of Aβ status at the group level, although regional MRI measurements and speech and language testing also performed well and could have advantages in predicting Aβ status in unclassified PPA subjects.

1. Introduction

Patients with primary neurodegenerative speech and language disorders can present either with primary progressive aphasia (PPA) (Mesulam, 2001; Gorno-Tempini et al., 2011) or progressive apraxia of speech (PAOS) (Josephs et al., 2012, 2013). The term PPA is reserved for a neurodegenerative disorder in which the most salient feature is language dysfunction (Mesulam, 1982, 2001). Three variants of PPA have been described which are each characterized by different patterns of language impairment (Gorno-Tempini et al., 2011). The agrammatic variant (agPPA) is characterized by written and verbal language that is grammatically flawed and sometimes with apraxia of speech (AOS);

the semantic variant (svPPA) is characterized by anomia and loss of single-word knowledge; and the logopenic variant (lvPPA) is characterized by anomia without loss of word knowledge, difficulty with sentence repetition and phonologic errors. In contrast, the term PAOS describes a neurodegenerative disorder in which AOS is the presenting and most dominant clinical feature (Josephs et al., 2012, 2013). These subjects can present with slow speech rate, articulatory distortions, distorted sound substitutions and segmentation of syllables in multisyllabic words or across words. Language impairment can be present, although it must be less severe than the AOS (Josephs et al., 2013).

The pathological underpinnings of the PPA variants and PAOS are variable, typically having either a variant of frontotemporal lobar degeneration (FTLD) or Alzheimer's disease (AD) (Kertesz et al., 2005; Josephs et al., 2006; Harris et al., 2013; Mesulam et al., 2014). Clinical diagnosis is relatively helpful in predicting pathology, with lvPPA subjects usually having AD pathology and PAOS, agPPA and svPPA subjects

usually having FTLD pathology (Josephs et al., 2006; Mesulam et al., 2014). However, discordant cases are common, with AD pathology, or beta-amyloid (Aβ) deposition on PET, observed in 18% of PAOS(Josephs et al., 2014), 0–30% of agPPA (Rabinovici et al., 2008; Leyton et al., 2011; Chare et al., 2014, Josephs et al., 2014) and 11–21% of svPPA (Rabinovici et al., 2008; Leyton et al., 2011; Chare et al., 2014; Josephs et al., 2014) cases. Conversely, up to 46% of some series of lvPPA subjects do not have AD pathology (Harris et al., 2013). In addition, a large proportion of subjects with language impairment does not fulfill diagnostic criteria for one of the PPA variants, and hence remain unclassified (Sajjadi et al., 2012; Mesulam et al., 2014; Wicklund et al., 2014). Other biomarkers are therefore needed that can help predict the presence of AD in PPA and PAOS and hence help guide potential treatments. The PPA variants and PAOS are each associated with specific patterns of atrophy (Gorno-Tempini et al., 2004; Josephs et al., 2012, 2013), although it is unknown whether these patterns vary according to the presence of AD pathology, particularly within PPA syndromes, and hence whether MRI could provide clues to the underlying pathology.

The aim of this study was to determine whether a model based on regional gray matter volume data measured from MRI could predict the presence of Aβ deposition on PET in PPA variants and PAOS. We also aimed to compare this MRI model to a model based on speech and language test data, and to determine whether either the MRI or clinical model could in fact do better than clinical diagnosis.

2. Methods

2.1. Subject recruitment

All subjects that presented with a predominant speech or language complaint and fulfilled diagnostic criteria for PPA (Mesulam, 2001) or PAOS (Josephs et al., 2012, 2013) were prospectively recruited from the Department of Neurology, Mayo Clinic, between July 1st 2010 and June 1st 2014. All subjects underwent a detailed neurological and speech and language evaluation, as previously described (Josephs et al., 2012), and diagnoses were rendered by consensus between two speech-language pathologists (JRD and EAS) after reviewing video recordings and speech-language test results for each subject. All diagnoses were made blinded to any neurological or neuroimaging findings. All subjects also underwent a volumetric MRI and an Aβ PET scan. The neurological and speech and language evaluations, MRI and PET scans were all performed within 72 h. A total of 143 subjects were recruited into the study. Four subjects were excluded because they either could not perform the MRI or the MRI was of poor quality. Of the remaining 139 subjects, 97 were diagnosed with a PPA variant (Gorno-Tempini et al., 2011) (15 agPPA, 13 svPPA, 53 lvPPA and 16 unclassified PPA, UCPPA)

and 42 were diagnosed with PAOS (Josephs et al., 2012, 2013), according to our previously published criteria (Botha et al., 2015). In three of the UCPPA subjects, anomia was the predominant feature, with fluent speech, but these subjects did not meet criteria for lvPPA or svPPA (two of these were Aβ (+)). We have previously classified these subjects as progressive fluent aphasia (Botha et al., 2015). Of the remaining UCPPA subjects, two resembled lvPPA but lacked phonological errors and/or repetition deficits (both Aβ (−)), two resembled lvPPA but had agrammatism (both Aβ (−)), one had impaired comprehension of sentences and loss of word meaning (Aβ (+)), and one subject (Aβ (−)) had prominent anomia with spared word and object meaning, together with AOS and dysarthria. In two UCPPA subjects, impairment was too severe to classify (both Aβ (−)) and, in five, impairment was so mild that discrepancies or patterns of impairment could not be appreciated (all Aβ (−)).

Apolipoprotein genotyping and assessment for the presence of progranulin (Baker et al., 2006) or microtubule associated protein tau mutations (Hutton et al., 1998), and C9ORF72 repeat expansions (Dejesus-Hernandez et al., 2011) were performed as previously described (Whitwell et al., 2012; Flanagan et al., 2015). The study was approved by the Mayo Clinic IRB. All patients consented for enrolment into the study.

2.2. Speech and language data

Fourteen speech and language tests were entered into the predictive model. These tests were selected to assess the presence or absence of each diagnostic feature of each clinical variant (Wicklund et al., 2014). The fourteen tests include the Token Test Part V (DeRenzi and Vignolo, 1962) to assess comprehension of complex sentences, the auditory word recognition subtest of the Western Aphasia Battery (WAB) (Kertesz, 2007) to assess single word comprehension, the reading and writing irregular and non-word subtests of the WAB to assess surface dyslexia or dysgraphia, the repetition subtest of the WAB to assess repetition, the informational content subtest of the WAB to assess single word retrieval in spontaneous speech, the Pyramids and Palm Trees (PPT) (Howard and Patterson, 1992) test to assess object knowledge, the Boston Naming Test (BNT) (Lansing et al., 1999) to assess confrontational naming, the Apraxia of Speech Rating Scale (ASRS) (Strand et al., 2014) to assess the severity of apraxia of speech, and the Motor Speech Disorders (MDS) (Yorkston et al., 1993) scale to assess motor speech production. The presence of agrammatism in speech and the severity of phonological errors (0 = none, 1 = mild, 2 = moderate, 3 = severe) was determined by consensus between two speech language pathologists (JRD and EAS).

Table 1
Subject demographics.

	Total cohort	Aβ (+)	Aβ (−)	P value Aβ (+) v Aβ (−)
N	139	58	81	NA
PiB SUVR	1.3 (1.2–2.0)	2.1 (2.0–2.3)	1.2 (1.2–1.3)	<0.001
Female gender, no. (%)	70 (50%)	32 (55%)	38 (47%)	0.34
Education, yrs.	16 (13–18)	15 (13–18)	16 (13–18)	0.63
Apolipoprotein e4, no. (%)*	38/120 (32%)	29/53 (55%)	9/67 (13%)	<0.001
Age at exam, yrs.	69 (61–73)	70 (60–74)	68 (62–73)	0.96
Age at onset, yrs.	66 (58–70)	65 (56–70)	66 (59–70)	0.59
Disease duration, yrs.	3.0 (2.0–4.5)	3.5 (3.0–5.0)	3.0 (2.0–4.0)	0.04
Mini-Mental State Examination, (/30)	28 (24–29)	24 (16–28)	29 (27–30)	<0.001
Clinical Dementia Rating Scale sum of boxes, (/18)	1.0 (0–3.0)	3 (1–4.6)	0.5 (0–1.5)	<0.001
Clinical dx., no. (%)				<0.001
agPPA	15 (11%)	1 (2%)	14 (17%)	
svPPA	13 (9%)	2 (3%)	11 (14%)	
lvPPA	53 (38%)	47 (81%)	6 (7%)	
UCPPA	16 (12%)	3 (5%)	13 (16%)	
PAOS	42 (30%)	5 (9%)	37 (46%)	

Data shown as median (inter-quartile range).