Aphasic variant of Alzheimer disease
Clinical, anatomic, and genetic features

ABSTRACT

Objective: To identify features of primary progressive aphasia (PPA) associated with Alzheimer disease (AD) neuropathology. A related objective was to determine whether logopenic PPA is a clinical marker for AD.

Methods: A total of 139 prospectively enrolled participants with a root diagnosis of PPA constituted the reference set. Those with autopsy or biomarker evidence of AD, and who had been evaluated at mild disease stages (Aphasia Quotient $\geq 85$), were included (n = 19). All had quantitative language testing and APOE genotyping. Fifteen had MRI morphometry.

Results: Impaired word-finding was the universal presenting complaint in the aphasic AD group. PPA clinical subtype was logopenic (n = 13) and agrammatic (n = 6). Fluency, repetition, naming, and grammaticality ranged from preserved to severely impaired. All had relative preservation of word comprehension. Eight of the 15 aphasic participants with AD showed no appreciable cortical atrophy at the individual level on MRI. As a group, atrophy was asymmetrically concentrated in the left perisylvian cortex. APOE e4 frequency was not elevated.

Conclusions: There is a close, but not obligatory, association between logopenic PPA and AD. No language measure, with the possible exception of word comprehension, can confirm or exclude AD in PPA. Biomarkers are therefore essential for diagnosis. Asymmetry of cortical atrophy and normal APOE e4 prevalence constitute deviations from typical AD. These and additional neuropathologic features suggest that AD has biological subtypes, one of which causes PPA. Better appreciation of this fact should promote the inclusion of individuals with PPA and positive AD biomarkers into relevant clinical trials.

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GLOSSARY

AD = Alzheimer disease; AQ = aphasia quotient; FDR = false discovery rate; FTLD = frontotemporal lobar degeneration; NAT = Northwestern Anagram Test; NAVS-SPPT = Sentence Production Priming Test of the Northwestern Assessment of Verbs and Sentences; NFT = neurofibrillary tangles; PPA = primary progressive aphasia; PPA-G = primary progressive aphasia agrammatic subtype; PPA-L = primary progressive aphasia logopenic subtype; PPA-S = primary progressive aphasia semantic subtype; SOB = sum of boxes; WAB-R = Western Aphasia Battery–Revised; WPM = words per minute.

Primary progressive aphasia (PPA) is diagnosed when language impairment arises in relative isolation and progresses to become the primary obstacle to daily functioning. Frontotemporal lobar degeneration (FTLD) and Alzheimer disease (AD) are its most common neuropathologic correlates. The primary pathology is frequently FTLD-tau in agrammatic subtypes (PPA-G), FTLD-TDP in semantic subtypes (PPA-S), and AD in logopenic subtypes (PPA-L).1

The goal of this report is to characterize the features of PPA associated with AD. Previous investigations were based on samples of convenience with aphasias of variable severity and language testing of limited coverage, especially in the domain of grammar. The current report is based on 19 individuals with a clinical diagnosis of PPA and with postmortem verification or amyloid-PET scans consistent with AD pathology. All participants were enrolled into a prospective project where language measures are quantitatively and uniformly assessed and where cortical morphometry is used to identify regions of peak atrophy. Only participants initially studied at mild stages of aphasia...
were included to emphasize the characteristic features of the early language disturbance and their anatomical correlates as close to disease onset as possible.

Several specific questions were addressed. First, is there justification for equating PPA-L with AD pathology? Second, are there measures of language function characteristic/pathognomonic of PPA associated with AD? Third, is there a consistent pattern of atrophy distribution in PPA associated with AD? Fourth, is the APOE genotype frequency in this group different from that seen in more typical amnestic forms of AD?

METHODS The reference set for this investigation consisted of 139 participants with PPA prospectively enrolled into a longitudinal project, with clinical subtype distribution of 32% PPA-G, 18% PPA-L, 23% PPA-S, and 27% unclassifiable by current diagnostic criteria. Twenty-seven have come to autopsy and an additional 61 have amyloid-PET determinations. Data from these 88 participants were reviewed to identify individuals who had postmortem or biomarker findings consistent with AD and mild aphasia (e.g., initial Western Aphasia Battery-Revised [WAB-R] aphasia quotient [AQ] ≥85). The AQ threshold eliminated individuals where all language functions become compromised and the pattern of the aphasia loses its specificity. Data from the 19 participants who fulfilled these 2 criteria were included in the analyses (figure 1). The PPA diagnosis was based on 3 core criteria: (1) progressive language disorder of recent onset not attributable to elementary motor or perceptual deficits; (2) absence of consequential impairments in episodic memory, visuospatial skills, or attributable to elementary motor or perceptual deficits; (2) absence of

Figure 1 Flowchart showing the selection of participants included in the analysis

Participants with PPA (N=139)

Excluded (n=51): No amyloid scan, CSF, evaluation or autopsy

Participants with PPA (n=88)

Excluded (n=66): Biomarker or postmortem findings not consistent with AD

Participants with PPA (n=22)

Excluded (n=3): Disease moderate to severe (AQ <85) at initial visit

Participants included in analysis with PPA (n=19)

AD = Alzheimer disease; AQ = aphasia quotient; PPA = primary progressive aphasia.

AD = Alzheimer disease; AQ = aphasia quotient; PPA = primary progressive aphasia.
The 19 individuals with PPA in this study were selected to have postmortem or in vivo biomarker evidence consistent with Alzheimer pathology. Four of the participants had a primary postmortem diagnosis of AD by National Institute on Aging-Alzheimer’s Association criteria. The remaining 15 had amyloid-PET with $^{18}$F-florbetapir, which showed elevated amyloid, defined as the mean cortical standardized uptake value ratio $\geq 1.10$ (cerebral-to-cerebellar), using previously described methods for processing. This threshold was recommended for detecting neuritic plaques indicative of underlying AD.

RESULTS All participants were right-handed and Caucasian. There were 11 men and 8 women. Symptom onset was under age 65 years in 14 (74%), with 8 reporting onset in the 50s. Daily living activities that did not depend on language were mostly preserved. The mean AQ was 90 $\pm$ 4 and the mean Clinical Dementia Rating sum of boxes (SOB) was 0.8 (range 0–3), with 16 PPA participants having SOB scores of $\leq 1$, indicating essentially preserved activities of daily living beyond those that had become difficult due to aphasia.

Individual language measures and subtypes. Impaired word-finding was the presenting complaint and a prominent finding at the initial clinical assessment of all of the PPA participants (table 1). Word-finding hesitation lowered word output fluency in some participants, but not in those who reacted to word-finding failures with lengthy circumlocutions. In fact, 2 individuals had WPM (fluency) scores higher than control values. In the other language measures, performance ranged from severely impaired to nearly intact (table 1). The one exception was single word comprehension, which was universally preserved, with a group mean performance of 96% $\pm$ 5%. Symptoms of apraxia of speech were present in 6/19 individuals (4 PPA-L, 2 PPA-G) but at a level of prominence that was overshadowed by the aphasia.

Thirteen of the participants (68%) were classified as PPA-L. This proportion would drop to 58% if the 2 patients with relatively preserved repetition but logopenic speech were considered unclassifiable. Six (32%) were classified as PPA-G. Table 2 provides examples of agrammatic statements from each of the 6 PPA-G participants and their performance scores on the noncanonical sentence production tasks (NAT-NAVS). Independent $t$ tests showed that the PPA-G group was more impaired than the PPA-L group in sentence repetition and their AQ ($p \leq 0.01$, uncorrected) but these differences were not significant with Bonferroni correction. The other measures did not reveal significant group differences (table 1).

MRI morphometry. Quantitative MRI morphometry was available for 15 participants (11 PPA-L, 4 PPA-G). The group atrophy map of the entire sample ($n = 15$) is shown in figure 2. Peak atrophy sites

### Table 1 Demographics and performance on language tasks

<table>
<thead>
<tr>
<th>Age at visit, y</th>
<th>Range</th>
<th>Mean $\pm$ SD</th>
<th>Range</th>
<th>Mean $\pm$ SD</th>
<th>Range</th>
<th>Mean $\pm$ SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>All PPA, ($n = 19$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>50–76</td>
<td>61 $\pm$ 7</td>
<td>50–76</td>
<td>62 $\pm$ 8</td>
<td>52–66</td>
<td>59 $\pm$ 5</td>
</tr>
<tr>
<td>Symptom duration at visit, y</td>
<td>1–9</td>
<td>4 $\pm$ 2</td>
<td>2–8</td>
<td>4 $\pm$ 2</td>
<td>1–9</td>
<td>5 $\pm$ 3</td>
</tr>
<tr>
<td>Education, y</td>
<td>12–20</td>
<td>17 $\pm$ 2</td>
<td>12–20</td>
<td>17 $\pm$ 2</td>
<td>13–19</td>
<td>16 $\pm$ 3</td>
</tr>
<tr>
<td>WAB-AQ</td>
<td>85–97</td>
<td>91 $\pm$ 4</td>
<td>87–97</td>
<td>92 $\pm$ 3</td>
<td>85–91</td>
<td>88 $\pm$ 2</td>
</tr>
<tr>
<td>Fluency as percentage of control</td>
<td>35–117</td>
<td>71 $\pm$ 22</td>
<td>35–117</td>
<td>72 $\pm$ 25</td>
<td>50–82</td>
<td>68 $\pm$ 12</td>
</tr>
<tr>
<td>Noncanonical sentence production</td>
<td>47–100</td>
<td>80 $\pm$ 15</td>
<td>70–100</td>
<td>86 $\pm$ 8</td>
<td>47–80</td>
<td>64 $\pm$ 16</td>
</tr>
<tr>
<td>Noncanonical sentence comprehension</td>
<td>73–100</td>
<td>92 $\pm$ 9</td>
<td>73–100</td>
<td>94 $\pm$ 8</td>
<td>80–100</td>
<td>87 $\pm$ 10</td>
</tr>
<tr>
<td>Repetition of phrases and sentences</td>
<td>54–94</td>
<td>78 $\pm$ 11</td>
<td>54–94</td>
<td>82 $\pm$ 10</td>
<td>61–83</td>
<td>68 $\pm$ 8</td>
</tr>
<tr>
<td>Object naming</td>
<td>47–98</td>
<td>84 $\pm$ 14</td>
<td>47–98</td>
<td>88 $\pm$ 13</td>
<td>58–93</td>
<td>77 $\pm$ 13</td>
</tr>
<tr>
<td>Single word comprehension</td>
<td>81–100</td>
<td>96 $\pm$ 5</td>
<td>81–100</td>
<td>96 $\pm$ 5</td>
<td>92–100</td>
<td>97 $\pm$ 3</td>
</tr>
</tbody>
</table>

Abbreviations: AQ = aphasia quotient; PPA = primary progressive aphasia; PPA-G = primary progressive aphasia agrammatic subtype; PPA-L = primary progressive aphasia logopenic subtype; WAB = Western Aphasia Battery.

*Numbers beyond 100 indicate hyperfluency in comparison with controls.
fort the group as a whole were concentrated within the lateral temporal cortex, especially the superior temporal gyrus and the adjacent temporoparietal junction of the left hemisphere. Additional patchy atrophy was detected in dorsolateral and medial prefrontal cortex, precuneus, and inferior temporal cortex. Atrophy patterns for the clinical PPA-L and PPA-G subgroups yielded no significant differences in a direct group comparison (FDR = 0.05).

Scans were also qualitatively assessed (M.-M.M.) at the individual level. Eight out of 15 individual scans had no appreciable cortical atrophy. Each of the remaining 7 showed distinctly asymmetric atrophy mostly encompassing temporoparietal components of the left hemisphere language network.

**APOE.** Five cases (1 PPA-G and 4 PPA-L) had the ε4 allele of *APOE.* Only one of these was homozygous. The remaining 14 (73%) had an ε3,3 genotype. At the Northwestern Alzheimer’s Disease Brain Bank, 26% of the control population (n = 190) has at least one ε4 allele, whereas this frequency increases to 59% in those with an amnestic dementia during life and AD at autopsy (n = 75). The 27% frequency of ε4 allele carriers in the 19 PPA participants with biomarker evidence or autopsy-confirmed AD reported in the current investigation is similar to control values. These data are consistent with previous reports suggesting the ε4 allele of *APOE* is not a risk factor for clinical PPA or AD pathology in PPA.

**DISCUSSION** This report is based on 19 participants with PPA with autopsy or biomarker evidence of Alzheimer pathology, examined in the mild stages of the disease at initial assessment. Results are therefore relevant to clinical decision-making at the time of initial evaluation.

The majority of the participants (68%) had been clinically classified as PPA-L, including 2 cases with logopenic speech but preserved repetition. The remaining participants were classified as PPA-G. These proportions are in line with those of an autopsy series of 58 PPA cases examined at various severity stages, in which 69% of all cases with AD pathology as the primary diagnosis had logopenic aphasia. These results seem at odds with another study, also of PPA participants with autopsy or biomarker evidence of AD, where a complete overlap with PPA-L was reported. However, in that study, grammatical ability was not reported and 5/14 participants presented with additional nonverbal memory impairments. Some of the participants in that study may, therefore, have qualified for a PPA-G diagnosis and others may have failed to fulfill the root diagnostic PPA criteria, which require a relative sparing of episodic memory.

The converse question of whether all PPA-L is associated with AD reveals equally complex relationships. In the series of 58 autopsies, for example, only 56% of PPA-L cases were associated with a primary neuropathologic diagnosis of AD. Investigations addressing this question with amyloid-PET scans have also yielded variable results. One study reported that 92% of PPA-L participants had positive amyloid scans. Two other studies reported lower rates of 66% and 69%, more in line with the autopsy results.

<table>
<thead>
<tr>
<th>Table 2: Examples of agrammatic statements from each of the 6 primary progressive aphasia agrammatic subtype participants and their performance scores on the noncanonical sentence production tasks (Northwestern Anagram Test-Northwestern Assessment of Verbs and Sentences) (% correct)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. “I going there. A lot of telephoning and receiving telephoning people.” (80%)</td>
</tr>
<tr>
<td>2. “We stopped to get gas and to go to restrooms. The clerk starting yelley about the key.” (47%)</td>
</tr>
<tr>
<td>3. “I wanted to go to NY and play with baby. She and I playing with us at play.” (57%)</td>
</tr>
<tr>
<td>4. “We have up to 3,000 engineers world throughout the globe.” (47%)</td>
</tr>
<tr>
<td>5. “Joyous yells were shouting to Mr. + Mrs. James to see the success of the kite.” (80%)</td>
</tr>
<tr>
<td>6. “I placed student is family to go to high school.” (77%)</td>
</tr>
</tbody>
</table>

**Figure 2** Group atrophy map (false discovery rate = 0.001) and quantitative morphometry for the 15 individuals with primary progressive aphasia.

DFC = dorsal frontal cortex; ITC = inferior temporal cortex; PC = precuneus; STG = superior temporal gyrus; TPJ = temporoparietal junction. Numbers below the heat map represent p values.
While there is evidence that PPA associated with AD is more likely to present as logopenic aphasia and that logopenic PPA is more likely to be associated with AD, there is no one-to-one correspondence. Neither individual measures of language impairment nor clinical subtyping into logopenic vs agrammatic variants can resolve the differential diagnosis. Fluency, repetition, naming, and grammatical ability in individuals with PPA and AD neuropathology, at least in the early stages, may range from preserved to severely impaired and MRI morphometry may initially show no obvious atrophy. Even the presence of speech apraxia, albeit of lesser salience than the aphasia, does not rule out the presence of AD. At the individual patient level, therefore, the nature of neuropathology in a logopenic patient would be difficult to resolve without biomarker evidence.

In the 7 cases with appreciable cortical atrophy on quantitative MRI, the common denominators were profound asymmetry favoring the left hemisphere and greater atrophy of lateral temporal cortex compared to medial temporal areas or the precuneus. The peak atrophy pattern for the group (figure 2) showed a distribution similar to previous reports of atrophy and hypoperfusion in PPA participants with autopsy or biomarker evidence of AD. The concentration of atrophy in the temporoparietal junction and adjacent superior temporal gyrus mirrors atrophy patterns of PPA-L and is in keeping with the greater representation of logopenic participants in the group atrophy map shown in figure 2. The asymmetrical atrophy distribution in our PPA cohort differs from typical amnestic forms of AD, which tends to arise later than the amnesia and play a much less conspicuous role in disrupting customary activities. The Alzheimer pathology associated with language impairments, mostly in the form of anomia. However, such language impairments tend to arise later than the amnesia and play a much less conspicuous role in disrupting customary activities.

The inclusion of 2 individuals with logopenic speech and relatively preserved repetition deficits under the PPA-L variant could be viewed as a limitation since this designation does not strictly follow the 2011 consensus criteria. The alternative would have been to categorize these 2 individuals as unclassifiable, which would decrease the percentage of PPA-L associated with AD and increase the number of PPA phenotypes associated with AD pathology. All in all, the same conclusion could be made; there is no unique correspondence between a single PPA phenotype and AD neuropathology.

Another potential limitation of this study is the reliance on amyloid-PET with florbetapir as the AD biomarker in 15 of the 19 participants. In individuals who had been imaged within 1 year of death, however, the same ligand was shown to offer better than 95% sensitivity and specificity for the postmortem detection of neuritic plaques characteristic of AD. It is also conceivable that some of the PPA participants with positive amyloid scans could have an additional FTLD pathology. In 58 consecutive PPA autopsies, such a double diagnosis was encountered in only 1 patient whose postmortem examination met criteria for both AD and FTLD-TDP. The probability that the biomarker-positive PPA participants in the current study were misclassified pathologically is therefore quite low. Furthermore, the 4 autopsy-verified participants were evenly split between the PPA-L and PPA-G phenotypes and would, by themselves, support the conclusion that there is no exclusive relationship between AD and logopenic PPA.

Typical late-onset amnestic AD is commonly associated with language impairments, mostly in the form of anomia. However, such language impairments tend to arise later than the amnesia and play a much less conspicuous role in disrupting customary activities. The current study addresses the entirely different phenotype of PPA where the aphasia is the first and most salient feature. The Alzheimer pathology associated with this phenotype has prominent features that set it apart from the typical amnestic form of this disease. (1) Onset is most commonly before age 65, perhaps explaining why the female predominance of typical AD is not present. (2) Peak atrophy shows an asymmetric predilection for the language-dominant left hemisphere and displays only partial overlap with the atrophy signature of typical AD. (3) As previously reported in

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**Table 3 Variants of Alzheimer disease (AD)**

<table>
<thead>
<tr>
<th>Variant Description</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Autosomal dominant, early-onset AD</td>
<td>Caused by amyloidopathy, not related to age or APOE.</td>
</tr>
<tr>
<td>2. Late-onset AD</td>
<td>Age and APOE4 related, amnestic phenotype, neurofibrillary tangles (NFT) emerge and reach highest densities in hippocampal-entorhinal complex according to Braak &amp; Braak staging patterns.</td>
</tr>
<tr>
<td>3. Primarily aphasic AD</td>
<td>Not age or APOE4 related. NFT can violate Braak &amp; Braak staging patterns by being more frequent in language than memory areas.</td>
</tr>
<tr>
<td>4. Primarily visuospatial AD (posterior cortical atrophy)</td>
<td>NFT can be more frequent in visual areas (Brodmann area [BA] 17, BA 18, and superior colliculus) than the hippocampal-entorhinal complex. Age and APOE dependency remain to be determined.</td>
</tr>
<tr>
<td>5. Primarily behavioral/executive (frontal-type) AD</td>
<td>NFT densities in frontal cortex can be greater than in the hippocampal-entorhinal complex. Age and APOE dependency remain to be determined.</td>
</tr>
</tbody>
</table>

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an autopsy series, the APOE ε4 allele is not a risk factor for the AD that causes PPA. (4) Learning disabilities, including dyslexia, are risk factors for PPA but not amnestic dementias.21,22 (5) Neurofibrillary tangles (NFT) can display atypical asymmetric distributions that violate the Braak and Braak pattern by favoring the left hemisphere.20 (7) TDP-43 neuritic amyloid plaques may be asymmetrically distributed, favoring the left hemisphere.20 (7) TDP-43 abnormalities, seen in at least 30% of typical AD cases, are not present in the AD pathology associated with PPA.33 These features indicate that the AD associated with PPA has temporal, anatomic, neuropathologic, and genetic factors that diverge from those of the far more common late-onset and amnestic forms of AD. As shown in table 3, AD can have several variants, some of which, like PPA, are nonamnestic.34–38 Individuals with these atypical nonamnestic manifestations tend to be excluded from AD clinical trials, where outcome measures are chosen to emphasize memory function. The advent of molecular biomarkers now makes it possible to identify a sizable contingent of such individuals with underlying AD pathology. Their inclusion in clinical trials will offer them equal access to novel agents and will require the introduction of new outcome measures designed to assess the relevant nonamnestic domain of the primary cognitive impairment.

**AUTHOR CONTRIBUTIONS**
M.-M.M. and E.R. contributed to conception and design of the study; A.M., B.R., J.S., K.C., D.C., S.W., C.T.K., E.B., M.-M.M., and E.R. collected and analyzed the data; M.M. and E.R. drafted the manuscript.

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