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Prevalence of Amyloid-β Pathology in Distinct Variants of Primary Progressive Aphasia

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Abstract

Objective: To estimate the prevalence of amyloid positivity, defined by positron emission tomography (PET)/cerebro-spinal fluid (CSF) biomarkers and/or neuropathological examination, in primary progressive aphasia (PPA) variants.

Methods: We conducted a meta-analysis with individual participant data from 1,251 patients diagnosed with PPA (including logopenic [lvPPA, n = 443], nonfluent [nfvPPA, n = 333], semantic [svPPA, n = 401], and mixed/unclassifiable [n = 74] variants of PPA) from 36 centers, with a measure of amyloid-β pathology (CSF [n = 600], PET [n = 366], and/or autopsy [n = 378]) available. The estimated prevalence of amyloid positivity according to PPA variant, age, and apolipoprotein E (ApoE) ε4 status was determined using generalized estimating equation models.

Results: Amyloid-β positivity was more prevalent in lvPPA (86%) than in nfvPPA (20%) or svPPA (16%; $p < 0.001$). Prevalence of amyloid-β positivity increased with age in nfvPPA (from 10% at age 50 years to 27% at age 80 years, $p < 0.01$) and svPPA (from 6% at age 50 years to 32% at age 80 years, $p < 0.001$), but not in lvPPA ($p = 0.94$). Across PPA variants, ApoE ε4 carriers were more often amyloid-β positive (58.0%) than noncarriers (35.0%, $p < 0.001$). Autopsy data revealed Alzheimer disease pathology as the most common pathologic diagnosis in lvPPA (76%), frontotemporal lobar degeneration–TDP-43 in svPPA (80%), and frontotemporal lobar degeneration–TDP-43/tau in nfvPPA (64%).

Interpretation: This study shows that the current PPA classification system helps to predict underlying pathology across different cohorts and clinical settings, and suggests that age and ApoE genotype should be considered when interpreting amyloid-β biomarkers in PPA patients.

Primary progressive aphasia (PPA) is a clinical syndrome characterized by progressive loss of language function in the setting of focal degeneration of the dominant-hemisphere language network.[1] Although first described in the late 19th century by Pick and Dejerine and Serieux, the notion of isolated, progressive aphasia in the context of a neurodegenerative condition only came to broader medical/scientific attention in 1982 with Dr Mesulam's

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Author Contributions

D.B. and R.O. designed the study and coordinated data sharing. D.B., C.G., P.J.V., and R.O. performed data analysis. D.B., M.L.G.-T., G.D.R., C.G., R.L., and R.O. drafted the manuscript. All authors contributed to the acquisition of data as well as data analysis, provided intellectual input to the manuscript, and approved its final version.

Potential Conflicts of Interest

Nothing to report

Additional supporting information may be found online in the Supporting Information section at the end of the article.

seminal observations.[2] Since then, the nosology of PPA has been a field of intense investigation. The first official set of criteria for PPA defined 2 variants—progressive nonfluent aphasia, and semantic aphasia and associative agnosia[3] —which were included under the rubric of frontotemporolobar degeneration (FTLD). As a consequence, amyloid-β (Aβ) pathology (a neuropathological hallmark of Alzheimer disease [AD]) observed at autopsy in patients with PPA[4–6] was initially considered a comorbid, age-related process.[7–9] In 2004, cluster analyses of clinical and anatomical data brought Gorno-Tempini and colleagues to define a third (logopenic) variant of PPA (lvPPA), which was predicted to be primarily due to AD.[10] The high prevalence of Aβ positivity in lvPPA was confirmed using molecular imaging,[11] contributing to its label as the "language variant of AD." However, other studies showed high prevalence of AD pathology at autopsy in progressive nonfluent aphasia and, to a lesser extent, in semantic dementia.[12–17] Inconsistencies between the newly described variant and existing PPA criteria—for instance the overlap between the 1998 Neary criteria for progressive nonfluent aphasia[3] and the initial descriptions of logopenic aphasia[10]—became a growing source of confusion for clinicians and researchers.

To improve uniformity of case reporting and reliability of research results, a comprehensive set of consensus criteria for PPA was published in 2011.[18] Based on specific language profiles, 3 distinct variants were proposed: a non-fluent variant (nfvPPA), characterized by effortful speech output, agrammatism, and apraxia of speech, with relative sparing of single-word comprehension; a semantic variant (svPPA), distinguished by loss of word and object meaning, with fluent and grammatically correct speech; and lvPPA, defined by the co-occurrence of word-finding difficulties and impaired sentence repetition.

Based on these updated criteria, clinicopathological studies have shown that AD pathology often underlies lvPPA, whereas nfvPPA and svPPA are typically caused by FTLD pathology.[19–25] However, despite the application of international consensus clinical criteria, the prevalence of Aβ pathology—either measured at autopsy[19–26] or using in vivo biomarkers such as cerebrospinal fluid (CSF) analysis or positron emission tomography (PET)[27–38]—remained highly variable in single-center studies of PPA variants: 57 to 100% in lvPPA, 0 to 46% in nfvPPA, and 0 to 33% in svPPA. Given an estimated prevalence of 3.0/100,000 inhabitants for PPA,[33] a multicenter approach is essential to overcome statistical power issues. We therefore performed an individual patient meta-analysis including 1,251 PPA patients from 36 dementia centers. The primary objective was to provide prevalence estimates of Aβ pathology (determined at autopsy, CSF, and/or PET) for each PPA variant. In secondary analyses, we evaluated relationships between Aβ positivity and the main risk factors for Aβ deposition, notably age and presence of an apolipoprotein E (ApoE) ε4 allele. Furthermore, in a subset of patients with autopsy data available, we assessed the prevalence of neuropathological substrates in the different PPA variants.

Patients and Methods

Participating Centers

We searched the MEDLINE and Web of Science databases for biomarker (i.e., PET and/or CSF) or autopsy studies in PPA patients. The search terms were *primary progressive aphasia or PPA combined with biomarkers, pathology, autopsy, neuropathology, cerebrospinal fluid,*

CSF, PET, PiB, Pittsburgh, florbetapir, AV-45, florbetaben, flutemetamol, amyloid, abeta, frontotemporal, and Alzheimer's disease. A total of 1,012 titles and abstracts were reviewed, resulting in 37 unique cohorts for which we contacted the study corresponding author to obtain primary data. In addition, we contacted principal investigators of dementia centers known to be involved in PPA/frontotemporal dementia research who had not (yet) publish a paper on the specific issue of Aβ pathology in PPA. In total, we asked 42 study contact persons to provide participant-level data on Aβ status, age, sex, education, handedness, ApoE ε4 status, Mini-Mental State Examination (MMSE) score, and Clinical Dementia Rating scale score. Six centers declined or did not respond, leaving participant-level data from 36 cohorts for analysis (Supplementary Table 1). We requested contributors to send both published and unpublished data. Informed consent was obtained from all patients or their assigned surrogate decision makers, and the institutional review boards for human research of the participating centers approved all studies.

Data Collection and Operationalization

Information on study procedures, extracted from the publication or provided by the study contact person, was used to create a common set of variables.

Patients

Patients had to fulfil core criteria for PPA (i.e., language impairment being the earliest and most prominent clinical feature and the principal cause of impaired activities of daily living at least during the first 2 years after disease onset).[8,18] Patients were classified by contributing centers according to the PPA consensus criteria[18] as lvPPA, nfvPPA, svPPA, PPA-mixed (PPA-M; fulfils criteria for multiple PPA variants), or PPA-unclassified (PPA-U; does not fulfil criteria for any specific variant despite meeting core criteria for PPA). Due to small sample sizes, we aggregated PPA-M and PPA-U into a single PPA-M/U group. Because current PPA consensus criteria were published in 2011,[18] we requested contributing centers to reclassify patients diagnosed before 2011 according to the current diagnostic framework by retrospectively reviewing patient charts, including clinical and imaging information (i.e., structural magnetic resonance imaging and/or ^{18}F-fluorodeoxyglucose [FDG]-PET), excluding Aβ bio-markers and autopsy results. All diagnoses were made locally using site-specific clinical workup. In line with the PPA consensus criteria,[18] structural and functional imaging could be used to refine the clinical diagnosis. To minimize circularity biases, we emphasized that contributors should provide their working diagnosis prior to obtaining amyloid PET or lumbar puncture. However, because this is a retrospective study, there is no reliable measure to verify whether this was respected for all cases.

PET and CSF Procedures

PET scans were dichotomized ($A\beta^+$ or $A\beta^-$) using quantitative thresholds or visual reads according to the method used at the study site. Likewise, CSF measurements were dichotomized ($A\beta^+/A\beta^-$) using center-specific cutoffs. Detailed PET and CSF procedures for all participating cohorts are presented in Supplementary Tables 2 and 3. When PET scanning was performed for clinical purposes, the PET readers were generally not blinded to the clinical diagnosis. In total, 93 patients had multiple measures of Aβ pathology available (62 PET + CSF, 19 PET + autopsy, 12 CSF + autopsy), yielding 92% concordance between

modalities. Patients were rated $A\beta^+$ if at least one of the modalities revealed presence of Aβ positivity.

Autopsy Data

Autopsy cases were assessed by certified neuropathologists following the National Institute on Aging (NIA)–Alzheimer's Association[39] or NIA-Reagan[40] guidelines for the neuropathologic assessment of AD. All centers provided a measure of amyloid pathology. In addition, some centers provided Braak stage and neuropathological diagnosis of AD. Patients were dichotomized ($A\beta^+/A\beta^-$) based on their Thal Aβ plaque score (i.e., Thal phase ≥ 3) and/or Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria (i.e., definite, probable, or possible AD, indicating moderate to frequent neuritic plaques). In 10 of 13 autopsy studies (234/378 patients), neuropatho-logical assessment also included screening for other pathologies, including tau pathologies (Pick disease [PiD], corticobasal degeneration [CBD], progressive supranuclear palsy [PSP][41]), TAR DNA-binding protein 43 pathologies (TDP-43; type A, B, or C[42]), α-synuclein (dementia with Lewy bodies [DLB][43]), cerebrovascular disease, argyrophilic grain disease, prions, and FTLD–fused in sarcoma (FUS). Some patients were analyzed prior to the discovery of TDP subtypes and were therefore coded TDP-unspeci-fied. Aβ pathology was considered "comorbid" when combined with another full-blown pathology (FTLD TDP, primary tauopathy) in the absence of semiquantitative neuritic senile plaque density (CERAD score) and neurofibrillary tangle severity/distribution (Braak stage) adding up to a "high" or "moderate" likelihood of AD.

Clinical Measures and Genetic Testing

The MMSE score (measure of global cognition) was available for 945 patients with PPA (76%). Information on ApoE genotype was available for 487 patients (39%). None of the participating centers' cohorts was enriched for positive ApoE4 status. Age and gender were available for 1,167 (93%) and 1,203 (96%) patients, respectively.

Statistical Analyses

We conducted a meta-analysis with individual participant data. Baseline characteristics were compared using analysis of variance, Fisher exact test, and Pearson chi-squared test where appropriate. Similar to previous meta-analyses,[36,44] generalized estimating equations (GEE; using SPSS v23.0; IBM, Armonk, NY) models were used to estimate probabilities for Aβ positivity. GEE were used because they allow analysis of binary-correlated data, hence participant-level data from all cohorts can be modeled while simultaneously accounting for patients within cohorts. A logit link function for binary outcome with an exchangeable correlation structure was assumed to account for within-study correlation. Analyses were conducted using the total study population, unless specified otherwise. The main analysis was performed with diagnosis and age as independent variables, adjusted for center effects. Age as entered as a continuous measure centered at the median. We tested 2-way interactions between variables, and these terms were retained in the model if they were significant by the Wald statistical test. ApoE ε4 status was added to the model in secondary analysis of a subset of patients (487/1,251). The slope for each PPA variant according to age was compared to those of probable (mostly amnestic-predominant) AD patients (n = 1,359)

and of cognitively normal individuals (n = 2,914), derived from our previous meta-analyses.[36,44]

The degree of heterogeneity in prevalence of amyloid positivity across cohorts was assessed using the I^2 statistic (generated by a random-effects meta-analysis in Stata v14; StataCorp, College Station, TX). An I^2 statistic value > 50% indicates substantial heterogeneity.[45] Significance level was set at 2-sided $\alpha = 0.05$. Prism version 6.0 (GraphPad, La Jolla, CA) was used for the figures.

Results

A total of 1,251 patients diagnosed with PPA (lvPPA, n = 443; nfvPPA, n = 333; svPPA, n = 401; PPA-M/U, n = 74) and a measure of Aβ pathology (CSF, n = 600; PET, n = 366; or autopsy, n = 378; 93 cases had ≥ 2 modalities) were included from 36 centers (Table 1).

Approximately one-third of these cases (425/1,251; 34%) were included in previous publications (see Supplementary Table 1).

Demographic and Clinical Data

The mean age at Aβ measurement was 67.3 ± 8.1 years in the total PPA cohort (see Table 1). Patients with svPPA were slightly younger than those with other PPA variants. Gender was equally distributed across all PPA variants, except in PPA-M/U, in which females were underrepresented (30/74; 40.5%). In all PPA variants, patients were on average highly educated (13.8 ± 4.5 years). Consistent with the general population (non–right-handedness in 8–10%[46]), 68 of 809 (8.4%) patients were left-handed or ambidextrous. Non–right-handedness was more prevalent in svPPA (10.8%) than in nfvPPA (4.7%; $p < 0.05$).

Prevalence of ApoE ε4 allele was higher in lvPPA (42.1%) than in svPPA (26.3%) and nfvPPA (20.2%), and higher in PPA-M/U (37.2%) than in nfvPPA. MMSE was lower in lvPPA (21.0 ± 6.1) and PPA-M/U (21.0 ± 5.5) than in svPPA (23.2 ± 6.1) and nfvPPA (24.0 ± 5.7).

Prevalence of Aβ Positivity according to Diagnosis

About one-half (43.4%) of all PPA patients were $A\beta^+$. The prevalence of Aβ positivity was greater in lvPPA (85.6%) than in nfvPPA (19.5%) and svPPA (15.7%; $p < 0.001$). Thirty-six of 74 (48.6%) PPA-M/U subjects were $A\beta^+$.

Prevalence of Aβ Positivity by Modality

Prevalence of Aβ positivity within PPA variants was consistent across all 3 modalities (all $p > 0.05$), except for a higher Aβ positivity in CSF than PET in svPPA ($p < 0.05$) and a trend toward higher Aβ positivity in PET than autopsy in lvPPA ($p = 0.09$; Fig 3). Ninety-three patients had an Aβ pathology measure derived from >1 modality, yielding a 92% concordance rate.

Prevalence of Aβ Positivity according to Age

The estimated prevalence of Aβ positivity across the age span for variants of PPA is presented in Table 2. In the total sample, $A\beta^+$ PPA patients were older than $A\beta^-$ PPA patients (68.4 ± 7.8 vs 66.4 ± 8.2, $p < 0.001$). Within PPA variants, $A\beta^+$ nfvPPA, svPPA, and PPA-M/U patients were older than their $A\beta^-$ counterpart patients (70.8 ± 8.3 vs 68.2 ± 8.3, 69.0 ± 6.5 vs 64.5 ± 7.7, 71.4 ± 7.4 vs 67.3 ± 8.6 years, all $p < 0.05$). GEE analyses revealed that Aβ positivity increased with age in nfvPPA and svPPA (β for change in prevalence per year ± standard error: 0.05 ± 0.02 [$p < 0.01$] and 0.08 ± 0.02 [$p < 0.001$], respectively), but not in lvPPA ($p = 0.94$) or PPA-M/U ($p = 0.09$; Fig 1). Of note, the slope for lvPPA patients closely resembled that of probable AD patients (n = 1,359),[36] whereas the slopes for svPPA and nfvPPA strongly overlapped with the slope for cognitively normal individuals (n = 2,914; see Fig 1).[44]

Prevalence of Aβ Positivity according to ApoE

Across PPA variants, ApoE ε4 carriers were more often $A\beta^+$ (58.0%) than noncarriers (35.0%, $p < 0.001$). Within diagnostic groups, GEE analyses revealed main effects of ApoE on prevalence of amyloid positivity in nfvPPA (β for difference in prevalence for carriers vs non-carriers ± standard error: 1.22 ± 0.55, $p < 0.05$) but not in lvPPA ($p = 0.54$), svPPA ($p = 0.06$), and PPAM/U ($p = 0.30$).

Autopsy Results in Distinct PPA Variants

Autopsy results were available for 357 PPA patients (99 lvPPA, 109 nfvPPA, 106 svPPA, and 43 PPA-M/U; Fig 2). Most patients with lvPPA had primary AD pathology (76%), followed by FTLD TDP pathology (14%, mostly type A) or FTLD tau pathology (5%; see Fig 3). nfvPPA patients showed the most heterogeneous pathology across PPA variants. Most patients with nfvPPA had FTLD with primary tau pathology (64%)—either CBD (29%), PSP (17%), or PiD (18%)—followed by FTLD TDP pathology (24%, mostly type A) or AD pathology (8%). The vast majority of svPPA patients had TDP pathology (80%; mostly type C [73%]), with some patients exhibiting tau (11%) or AD (5%) pathology. PPA-M/U was divided between FTLD tau (35%), FTLD TDP (21%), and AD (42%) pathologies. The presence of FTLD tau, FTLD TDP-C, and AD pathology was associated with particular PPA phenotypes; 77 of 78 (99%) of FTLD TDP-C patients had a clinical diagnosis of svPPA, 75 of 107 (70%) AD^+ cases had lvPPA, and 70 of 102 (69%) FTLD tau cases had nfvPPA. In contrast, FTLD TDP type A pathology was associated with heterogeneous language profiles (among 35 TDP-A^+ cases, 10 were lvPPA, 16 nfvPPA, 1 svPPA, and 8 PPA-M/U). Aβ pathology was often comorbid (rather than the causative etiology) to primary tau/TDP pathology in nfvPPA (10/19 [53%] $A\beta^+$ cases) and svPPA (5/10 [50%]), but not in lvPPA (5/79 [6%]) and PPA-M/U (4/22 [18%]). Some cases of PPA exhibited atypical pathologies such as Creutzfeldt–Jakob disease (2/357), DLB (9/357), argyrophilic grain disease (1/357), vascular dementia (1/357), FTLD FUS (1/357), and globular glial tauopathy (2/357).

Assessment of Study-Related Heterogeneity

According to the I^2 statistic, there was no substantial heterogeneity in the prevalence of Aβ positivity between centers for any of the diagnostic groups (lvPPA [29.6%, $\chi^2 = 42,64$], nfvPPA [28.9%, $\chi^2 = 37.96$], svPPA [13.5%, $\chi^2 = 33.53$], PPA-M/U [2.2%, $\chi^2 = 12.27$], all $p > 0.05$).

Discussion

In this multicenter study involving 1,251 patients diagnosed with PPA and a measure of Aβ pathology (CSF, PET, or autopsy), we found that Aβ positivity is more prevalent in lvPPA (86%) than in nfvPPA (20%) or svPPA (16%). The prevalence of Aβ positivity increased with advancing age in nfvPPA and svPPA (similar to cognitively normal subjects[44]), but not in lvPPA (in line with probable AD patients[36]). Furthermore, svPPA and nfvPPA patients carrying a major risk allele for sporadic AD (i.e., ApoE ε4) were more often $A\beta^+$ than noncarriers. These results demonstrate the utility of the new classification system[18] to predict underlying pathology of PPA in various clinical settings and suggest that age and ApoE genotype should be considered when interpreting Aβ biomarkers in PPA patients.

In previous individual studies, the prevalence of Aβ pathology detected using in vivo biomarkers or neuropatho-logical examination in patients with distinct variants of PPA differed widely: 57–100% in lvPPA, 0–46% in nfvPPA, and 0–33% in svPPA.[19–26,38] This meta-analysis using individual participant data from 36 centers showed that Aβ pathology was present in the vast majority of patients with lvPPA (86%) and in a minority of nfvPPA (20%) and svPPA (16%) cases. Furthermore, autopsy data from 357 PPA patients revealed that AD pathology was the major driving force in lvPPA (76%), whereas FTLD TDP-43 (80%, mostly type C) and FTLD tau (64%) pathology where most prevalent in svPPA and nfvPPA, respectively. These findings are consistent with the notion of selective vulnerability of neural networks to specific proteinopathies, with AD pathology having a tropism toward posterior temporoparietal brain regions, tau pathology toward frontostriatal networks, and TDP-C pathology toward the temporal pole.[19,47,48] When these pathologies demonstrate lateralization toward the language-dominant hemisphere, this may result in distinct variants of PPA (lvPPA, nfvPPA, or svPPA, respectively). The mechanisms underlying lateralization of pathology in PPA remain a mystery. It has been suggested that left-handedness or developmental learning disabilities (eg, dyslexia) may increase vulnerability of the language-dominant hemisphere to neurodegenerative disorders.[49,50] In this multicenter study, the proportion of non–right-handedness was similar among PPA variants and consistent with the general population,[46] and there were no data available for learning disabilities. However, handedness data were only available in 25 of 36 centers for 809 of 1,251 patients (65%) and were not evaluated thoroughly using a handedness questionnaire, hence forced right-handedness may be a potential confounder.[51] Genome-wide association studies might shed light on potential contributors to dominant-hemisphere vulnerability in PPA. Similarly, a recent genome-wide association study in posterior cortical atrophy (the “visual variant of AD”) revealed associations with genes involved in neurodevelopment of the visual system and retinal degeneration.[52]

This study highlights that caution is needed in interpreting the significance of amyloid biomarkers in PPA. Several findings suggest that Aβ pathology may be an age-related process in svPPA and nfvPPA, comorbid to primary FTLD pathology (i.e., TDP-43 or 3R/4R tau). First, there is a strong increase of Aβ positivity in clinical syndromes mostly associated with non-AD pathologies (i.e., nfvPPA and svPPA) with the presence of 2 main risk factors for sporadic AD (i.e., aging and ApoE ε4). Second, the slopes of increased Aβ positivity according to age in nfvPPA and svPPA (see Fig 2) bear strong resemblance with that of cognitively normal elderly subjects.[44] Finally, our autopsy results showed that more than one-half of $A\beta^+$ nfvPPA/svPPA patients exhibit concomitant FTLD pathology, compared to only 6% of $A\beta^+$ lvPPA patients (see Fig 3), which is consistent with several case reports showing that positive Aβ biomarkers do not necessarily indicate that the clinical syndrome is primarily driven by AD pathology.[53–55] Previous reports have shown that ApoE4 allele was a risk factor for amyloid positivity but not for neuropathological diagnosis of AD in PPA patients.[12,23,25] This has potential clinical ramifications, as the increased a priori likelihood of detecting (comorbid) Aβ pathology in older patients and/or ApoE ε4 carriers should be considered when interpreting Aβ biomarkers in patients with PPA. For example, in older patients with a clear clinical profile of nfvPPA or svPPA, a positive amyloid PET should be interpreted with caution, as amyloid PET has lower positive predictive value for AD neuropathology in such patients.[55,56] Conversely, it is possible that comorbid age-related Aβ pathology may not be an innocent bystander, as recent data suggest that it is associated with worse cognition and greater probability of clinical expression of different dementia syndromes.[36,57,58]

Apart from the possibility of dual pathologies, there are several other explanations for diverging biomarker results in PPA (eg, $A\beta^-$ lvPPA or $A\beta^+$ nfvPPA/svPPA). First, the imperfect clinicopathological correlations in PPA may reflect the incomplete tropism of pathogenic proteins for specific brain networks, as proteinopathies sometimes arise in nodes outside their typical “signature” networks.[47,48] Recent studies showed that $A\beta^+$ and $A\beta^-$ lvPPA patients showed differential clinical features and hypometabolic deficits at [^{18}F]FDGPET, suggesting that deeper clinical/anatomical phenotyping of lvPPA patients could help better predict the underlying pathology.[35,59,60] Second, the in vivo biomarkers could possibly have provided false-positive or false-negative results. This is likely only a partial explanation, however, as Aβ PET and CSF assessments correspond well with neuropathological examination,[61,62] and the 3 modalities provided similar results in this study. Finally, imperfect clinicopathological correlations could be attributed to clinical misdiagnosis and/or variable interpretation of the clinical criteria. The implementation of standardized tests to assess key language features of PPA (eg, repetition, agrammatism, comprehension) might help increase interrater reliability of PPA diagnosis. For instance, patients with lvPPA may successfully repeat short/simple sentences (and hence be diagnosed with PPAU), yet would show impairment at more complex repetition tasks.[26,34,63]

The consensus criteria for PPA captured the vast majority of language profiles of patients in this study. Only 5.9% of PPA could not be classified into 1 of the 3 variants, either because they had unclassifiable (n = 40) or mixed (n = 34) phenotypes. The unclassifiable phenotype primarily included patients with word retrieval and naming deficits who did not fit a diagnosis of lvPPA due to not meeting the core criterion of abnormal repetition. Most

patients with a mixed phenotype exhibited core features of multiple PPA variants, for instance, a combination of agrammatism and word comprehension deficits. Likewise, some patients who fit the semantic or agrammatic classification also fulfilled criteria for lvPPA. The prevalence of mixed/unclassifiable phenotypes is consistent with most large cohorts published to date,[19,22–24,33,38] but lower than others.[64–67] The heterogeneous pathologies found at autopsy of PPA-M/U subjects suggest that the ambiguities in the current PPA classification cannot be easily resolved through the addition of a fourth clinical variant. Of note, patients with a pure phenotype of primary progressive apraxia of speech[68] were not included in the study if they did not fulfill core criteria for PPA. Many included nfvPPA patients were reported to have predominant apraxia of speech, yet still exhibited language impairments (agrammatism, writing/reading difficulties) consistent with PPA. Finally, MMSE scores were lower in lvPPA (21.0 ± 6.1) and PPA-M/U (21.0 ± 5.5) than in svPPA (23.2 ± 6.1) and nfvPPA (24.0 ± 5.7). This is consistent with previous reports suggesting that patients with PPA due to AD have greater memory, visuospatial, and executive impairment than other PPA variants.[69–72]

Strengths of this study include the large sample size (n = 1,251) from 36 centers, and the inclusion of various measures of Aβ pathology (CSF, PET, and autopsy). Our study also has limitations. First, due to the retrospective nature of the study, there remains an inherent risk for circularity biases, with biomarker results influencing diagnostic classification (or vice versa) due to assumptions regarding clinicopathological correlations. Although we emphasized that coinvestigators provide patients' working diagnosis prior to the biomarker study (i.e., agnostic to Aβ status), we cannot reliably confirm that this was respected at all centers. Likewise, as some scans were performed on a clinical basis—hence readers were not blinded to the clinical diagnosis—we cannot exclude that knowledge of clinical diagnosis has influenced PET visual interpretation in some borderline cases. Prospective studies are needed to mitigate these potential circularity biases. Second, differences in clinical workup across centers—with variable use of neuropsychological assessment, speech/language pathology, and structural and functional imaging—likely had an influence on patients' classification. Uniformly applied, research-level phenotyping of PPA patients would likely have resulted in stronger clinicopathological correlation.[19,38] Nevertheless, our study was able to assess the current classification system across a diverse spectrum of clinical settings. Third, acquisition and interpretation methods for PET and CSF were not harmonized across cohorts (eg, different PET tracers, CSF analytical steps, neuropathological procedures). We addressed this using center- or method-specific cutpoints and corrected for center effects. Importantly, I^2 statistics did not reveal significant study-related heterogeneity between centers. Furthermore, post hoc analyses showed no significant differences across modalities. Fourth, when interpreting this study, some sample characteristics should be considered. For example, most patients visited tertiary referral centers and patients were highly educated (13.8 years on average). Finally, because the majority of PPA research focused on the FTLD spectrum, ApoE genotype information was only available in ~40% of the sample.

In conclusion, this multicenter study helps to refine our understanding of clinicopathological correlations in PPA. In future studies, further investigations of clinical, structural/functional imaging, and genetic features of PPA are needed to increase our knowledge of PPA

pathogenesis. This will improve accuracy of the PPA diagnosis and the identification of the underlying etiology, which will lead to more accurate and efficient participant inclusion in clinical trials with disease-modifying agents tailored to reduce cerebral Aβ, tau, and/or TDP-43 pathology. Furthermore, the field would benefit from a prospective multicenter trial assessing the potential benefit of cholinesterase inhibitors in lvPPA and other $A\beta^+$ PPA variants. As with most rare disorders (prevalence = 3.0/100,000), PPA will benefit from tight collaboration between researchers worldwide to obtain sufficient sample size.

Supplementary Material

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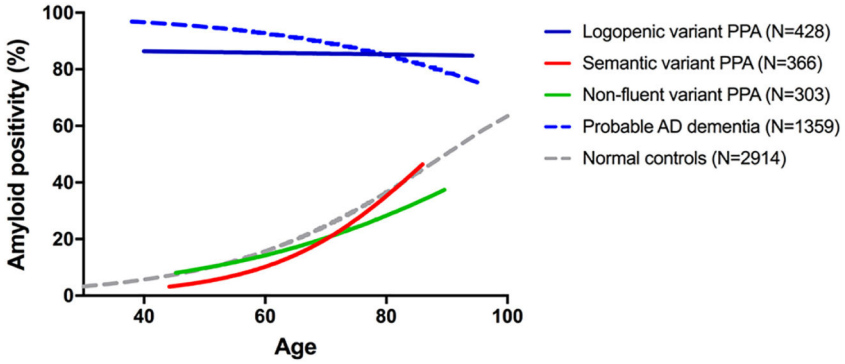
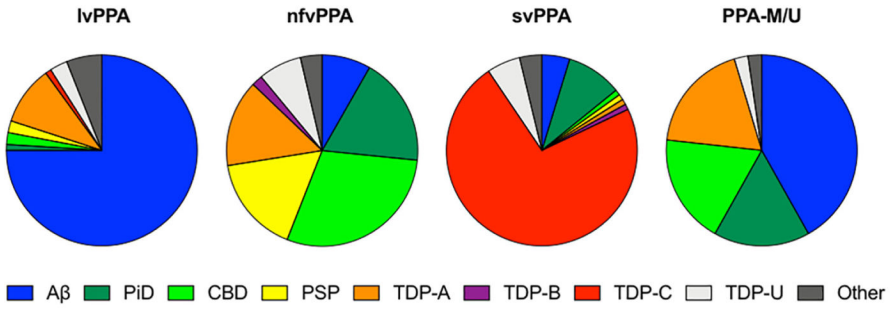


FIGURE 1:

Prevalence of amyloid-β pathology in primary progressive aphasia (PPA) variants by modality. Ninety-three patients had multiple measures of Aβ pathology available (62 positron emission tomography [PET] + cerebrospinal fluid [CSF], 19 PET + autopsy, 12 CSF + autopsy), yielding 92% concordance between modalities. CSF = cerebrospinal fluid; lvPPA = logopenic variant of PPA; nfvPPA = nonfluent variant of PPA; PET = positron emission tomography; PPA-M/U = mixed/unclassified PPA; svPPA = semantic variant of PPA.

A



B

Variant	Amyloid-β		FTLD Tau			TDP-43				Other
	Primary	Co-morbid	PiD	CBD	PSP	TDP-A	TDP-B	TDP-C	TDP-U	
lvPPA (n=99)	75	5	1	2	2	10	-	1	3	CJD, DLB (4), VaD
nfvPPA (n=109)	9	10	20	32	18	16	2	-	8	CJD, DLB (2), FTLD-FUS
svPPA (n=106)	5	5	10	1	1	1	1	77	6	AGD, DLB, GGT (2)
PPA-M/U (n=43)	18	4	7	8	-	8	-	-	1	DLB (2)
Total (n=357)	107	23	38	43	21	35	3	78	18	AGD, CJD (2), GGT (2), DLB (9), VaD, FTLD-FUS

FIGURE 2:

Prevalence of amyloid-β positivity in primary progressive aphasia (PPA) variants. Prevalence estimate of amyloid-β positivity is based on generalized estimating equations analyses. Data for normal controls and typical Alzheimer disease (AD) dementia come from the Amyloid PET Study Group.[36,44]

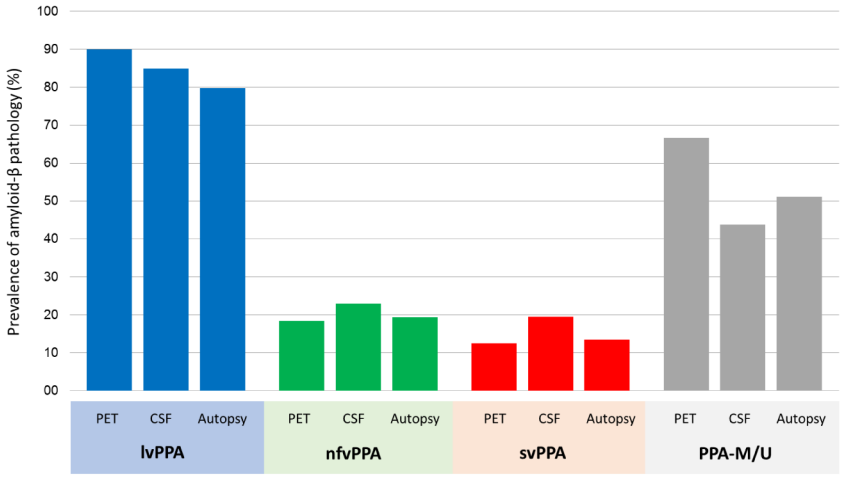


FIGURE 3:

Autopsy results. (A) Pie charts showing the respective prevalence of amyloid, tau, TAR DNA-binding protein 43 (TDP), and other pathologies in primary progressive aphasia (PPA). (B) Breakdown of the different pathologies for each PPA variant. Aβ = amyloid-β; AGD = argyrophilic grain disease; CBD = corticobasal degeneration; CJD = Creutzfeldt–Jakob disease; DLB = dementia with Lewy bodies; FTLD = frontotemporolobar degeneration; FUS = fused in sarcoma; GGT = globular glial tauopathy; lvPPA = logopenic variant of PPA; nfvPPA = nonfluent variant of PPA; PiD = Pick disease; PPA-M/U = mixed/unclassified PPA; PSP = progressive supranuclear palsy; svPPA = semantic variant of PPA; VaD = vascular dementia.

TABLE 1.

Patients' Demographics

Characteristic	lvPPA, n = 443	nfvPPA, n = 333	svPPA, n = 401	PPA-M/U, n = 74	All PPA, n = 1,251
Age, mean yr (SD)	67.6 (7–9)[a]	68.7 (8.4)[b]	65.3 (7.7)	69.3 (8.3)	67.3 (8.1)
Age, median yr (range)	68 (40–94)	69 (45–90)[b]	65 (44–86)	71 (49–83)	67 (40–94)
Age groups, n (%), y					
<50 years	1 (0)	3 (1)	5 (1)	1 (1)	10 (1)
50–59 years	73 (17)	37 (12)	82 (22)	9 (12)	201 (17)
60–69 years	176 (41)	121 (40)	181 (50)	21 (28)	499 (43)
70–79 years	153 (36)	118 (39)	86 (24)	32 (43)	389 (33)
≥80 years	25 (6)	24 (7)	12 (3)	7 (10)	68 (6)
Sex, % female	48.0	46.2	53.6	40.5	49.0
Education, mean yr (SD)[c]	13.8 (5.2)	13.7 (4.0)	13.7 (4.0)	13.5 (4.2)	13.8 (4.5)
MMSE score, mean (SD)	21.0 (6.1)	24.0 (5.7)[d]	23.2 (6.1)[e]	21.0 (5.5)	22.5 (6.1)
Handedness, % non—right-handed	8.1	4.7	10.8[f]	12.8	8.4
ApoE4, carrier/noncarrier (% positive)	67/92 (42.1)[a,g]	26/103 (20.2)	41/115 (26.3)	16/27 (37.2)	150/337 (30.8)
Modality, % PET/CSF/autopsy	34[a]/52[g]/22	33[b]/39/37[b,d]	26/51[f]/28	4/43/58	29/48/30

Interval variables were compared using independent samples *t* tests, and nominal variables using Fisher exact or Pearson chi-squared tests. Group comparisons between PPA-M/U and the other groups are not included.

[a] lvPPA > svPPA.

[b] nfvPPA > svPPA.

[c] Mann–Whitney *U* test performed.

[d] nfvPPA > lvPPA.

[e] svPPA > lvPPA.

[f] svPPA > nfvPPA.

[g] lvPPA > nfvPPA.

ApoE = apolipoprotein E; CSF = cerebrospinal fluid; lvPPA = logopenic variant of PPA; MMSE = Mini-Mental State Examination; nfvPPA = nonfluent variant of PPA; PET = positron emission tomography; PPA = primary progressive aphasia; PPA-M/U = mixed/unclassified PPA; SD = standard deviation; svPPA = semantic variant of PPA.

TABLE 2.

Prevalence of Amyloid-β Pathology in PPA Variants across Age Groups

Age, yr	lvPPA	nfVPPA	svPPA	AD	Controls
50					
n	17	21	25	63	426
Prevalence	86	10	6	95	10
95% CI	72–94	5–20	3–10	91–97	7–14
60					
n	131	79	156	373	618
Prevalence	86	15	11	93	16
95% CI	77–92	10–23	7–16	90–95	12–20
70					
n	200	129	137	505	1,097
Prevalence	86	20	19	90	25
95% CI	80–90	15–27	14–25	87–92	20–29
80					
n	71	66	45	356	643
Prevalence	85	27	32	85	37
95% CI	78–90	20–36	22–43	81–89	31–43
90					
n	9	8	3	62	129
Prevalence	85	35	46	79	50
95% CI	72–93	23–49	30–62	70–85	41–59
All					
n	428	303	366	1,359	1,614
Prevalence	86	18	15	89	24
95% CI	76–91	13–34	10–29	86–92	19–29

Number of participants for each age group: 50 (≤54), 60 (55–64), 70 (65–74), 80 (75–84), 90 (≥ 85) and total (all ages). Estimated prevalence (95% CI) across groups are derived from generalized estimating equation models, adjusted for study effects, and only displayed if n ≥ 3.

AD = Alzheimer disease; CI = confidence interval; lvPPA = logopenic variant of PPA; nfvPPA = nonfluent variant of PPA; PPA = primary progressive aphasia; svPPA = semantic variant of PPA.