Clinical comparison of progressive aphasia associated with Alzheimer versus FTD-spectrum pathology

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Abstract

Objective: Recent post-mortem studies indicate that 30-40% of patients with clinically diagnosed progressive aphasia (PA) have AD pathology, while the remainder have pathology in the FTD spectrum. This study aimed to compare the clinical features of patients from these two groups.

Materials & Methods: A retrospective chart review was conducted on 33 pathologically verified PA patients: n=13 AD and n=20 FTD-spectrum pathology. Demographics, global cognitive function, non-verbal memory, neuropsychiatric symptoms and structural imaging were compared between the two pathology-confirmed groups.

Results: Median survival was 6.3 years in the FTD group versus 8.1 years in the AD group, in spite of the fact that onset for AD was on average 2.0 years older than FTD. Features highly specific in predicting FTD-spectrum pathology were age-of-onset before 60 years, preference for sweet food, disinhibition and focal knife-edge frontotemporal atrophy, although sensitivity for each of these was remarkably low (highest sensitivity was 45% for disinhibition). Some clinical features hypothesized to distinguish AD from FTD-spectrum pathology, such as global functional impairment within two years of onset and poor non-verbal memory ability, were not useful in separating the two groups.

Conclusions: If present, certain clinical and imaging features can help to identify PA with FTD-spectrum pathology, notably the presence of the neuropsychiatric features seen with behavioural presentations of FTD and knife-edge atrophy on structural imaging. The profile of non-linguistic cognitive deficits does not appear discriminating though prospective studies are needed to evaluate this issue further.
Introduction

Progressive non-fluent aphasia (PA) is a clinical syndrome defined by consensus criteria,[1] of slow, effortful speech production characterized by anomia plus phonological and grammatical errors. Single word comprehension and non-linguistic cognitive functions are relatively preserved in the early stages. PA is one of the clinical subgroups of frontotemporal lobar degeneration (FTLD), the others being semantic dementia (SD) and behavioural variant frontotemporal dementia (bvFTD). Histopathologically, clinical FTLD can be associated with tau-positive inclusions (including classic Pick’s disease as well as pathology consistent with progressive supranuclear palsy or corticobasal degeneration); ubiquitin-positive inclusions (including overlap cases with motor neuron disease); and cases with neither tau nor ubiquitin inclusions (dementia lacking distinctive histology, DLDH).[2] A growing number of studies, however, indicate that approximately one third of cases with the clinical syndrome of PA have AD pathology at necropsy.[3-5] This does not appear to be the case with the other FTLD syndromes—in one study, the rate of AD pathology was 44.1% in PA compared to only 7.1% of clinical bvFTD and 10% of SD.[4] Comparable findings were reported in a separate study in which PA was subsumed under the label of ‘primary progressive aphasia’. The pathological heterogeneity of clinical PA poses a challenge to accurate prediction of pathology in vivo. More recently, a subordinate PA syndrome called ‘logopenic aphasia’ (LPA) has been described, the salient features of which are slow speech with anomia and word-finding pauses, while production of grammar, articulation and single-word comprehension are relatively spared.[6] Amyloid ligand imaging suggests that Alzheimer pathology is the most probable diagnosis in this group.[7, 8] Although LPA is a fluent aphasia in the grammatical sense, word finding pauses can lead to a slowing of speech output; a separation of PA into PNFA (agrammatic) and LPA (anomic) has been proposed.[9]

In pragmatic terms, improving clinical prediction of underlying pathology need not focus exclusively on linguistic features in PA. For instance, a nuclear imaging study reported that hypofunctioning of bilateral temporo-parietal association cortex (TPA)—as is found in clinical AD—was highly specific in predicting AD pathology in clinically diagnosed PNFA, while normal TPA perfusion or metabolism was highly specific for FTD-spectrum pathology.[10] Although this finding provided the possibility to predict AD-pathology with standard diagnostic tests in PA in vivo, the sensitivity of nuclear imaging was low. The aim of the present study, therefore, was to search retrospectively for other clinical features that might discriminate AD from FTD-spectrum pathology. Using post-mortem pathological diagnosis as the gold standard to divide patients into AD versus FTD-spectrum pathology groups, we compared demographic, general neuropsychological, neuropsychiatric and structural imaging features. Although new techniques such as amyloid-ligand imaging offer the potential to classify patients accurately into AD and FTD-spectrum pathology,[11] such techniques are presently restricted to research settings. Should these procedures find clinical application in the future, cost and availability will keep them out of reach of many cognitive disorders clinics. Similarly, although the LPA syndrome suggests that certain linguistic features
might have predictive value for AD pathology, diagnostic sensitivity and specificity for such features are not yet available. Moreover, it is unclear whether all patients with PA can be accommodated within a binary classification of PNFA and LPA. Identification of general clinical predictors of pathology in PA therefore remains relevant.

Methods

**Case ascertainment:** PA cases were identified retrospectively from the local Brain Bank database. These were patients who had attended the Cognitive Disorders Clinics at Addenbrooke’s Hospital, Cambridge, between 1990-2008 and had consented to post-mortem tissue donation. The research program was approved by the Addenbrooke’s Hospital Local Research Ethics Committee. Criteria for PA were (i) an insidious onset, gradually progressive loss of language fluency as the primary presenting syndrome; (ii) effortful, distorted (or dysprosodic) speech output; (iii) phonological errors in conversation and/or repetition; (iv) preservation of single content-word comprehension. The study did not include patients whose loss of fluency appeared to be driven by word-finding pauses alone. All cases had been diagnosed as “PNFA” in life but, because this was a retrospective review, it was not always possible to be certain that cases pre-dating the description of LPA might not have had features more closely aligned to this latter syndrome. In particular, recent conceptualisation of LPA proposes that phonological errors may be part of the syndrome and such errors had always been considered a prominent feature in the local diagnostic formulation of PNFA.[9] As such the term “PA” is used in this study. Finally, in order to avoid biasing the results, less severe symptoms in other cognitive domains, such as memory, were not considered exclusion criteria. A total of 33 patients were identified, including 26 patients reported in an earlier clinicopathological study.[4]

**Data collection**

1/ **Demographics and clinical features:**
Age at first presentation and death, and years of education, were noted. Age of onset was estimated according to the caregivers’ reports at the first clinic attendance. Measures of clinical features, including global cognitive function, activities of daily living and neuropsychiatric symptoms, were obtained from the case records. These records had been systematically compiled in a clinical research-focused environment with particular specialist interest in documenting the features of neurodegenerative cognitive and behavioral syndromes. In latter years these records were further supplemented by care-giver rating questionnaires regarding cognition, behaviour and functional abilities (Cambridge Behavioural Inventory, CBI) and neuropsychiatric symptoms (Neuropsychiatric Inventory, NPI).[12, 13] Activities of daily living (ADLs) were assessed with reference to the patients’ abilities in bathing, continence, dressing, feeding, going to the toilet and finding their way independently in and around the home. Impaired global cognitive function was defined as impairment in multiple cognitive domains on
neuropsychological evaluation and an MMSE score of \( \leq 23/30 \). As different neuropsychological test batteries were used during the 19 year recruitment period, we were unable to contrast test performance directly and were, instead, limited to a simple binary classification of “impaired” vs. “preserved” global function. Specifically assessed neuropsychiatric behaviours included exacerbated preference for sweet food, disinhibition, apathy and depression. These four features were chosen because previous research has suggested that sweet food preference and disinhibition have specificity for FTD; apathy is extremely prevalent in FTD; and lack of insight in FTD is suggested to be associated with less depression.\(^{12, 14}\)

2/ Visuospatial ability and non-verbal memory
Rey figure copy and delayed recall after 30 minutes, as measures of visuospatial ability and non-verbal memory,\(^{15}\) were available from the first examination in 25 patients (AD \( n=11 \); FTD-spectrum \( n=14 \)).

3/ Structural imaging
Structural imaging from the original clinical work-up was available in 21 patients (magnetic resonance imaging in 20; computerized tomography in one): six with AD, and 15 with FTD-spectrum, pathology. Previous reports have suggested that disproportionate and, particularly, asymmetric frontotemporal atrophy has predictive value in discriminating FTD from AD.\(^{16-18}\) Visual ratings of scans, blinded to pathological group and clinical details, were conducted. Scans were rated for the presence or absence of unequivocal disproportionate, and/or asymmetrical, frontal and/or temporal lobe atrophy (so-called ‘knife-edge’ atrophy). Inter-rater and intra-rater reliability were both 95.2%; in each case disagreement involved the same single subject (an FTD-spectrum patient); there was complete agreement in the ratings for the cases identified as having AD pathology.

4/ Confrontation naming
Although the aim of this study was to identify general clinical features that predict pathological diagnosis rather than to compare language profiles, scores on confrontation naming were available in \( N=25 \) patients (\( n=10 \) AD; \( n=15 \) FTD-spectrum) and so are included here. The Cambridge-devised naming test used in our research programme was altered during the period from which the current cohort of cases was sampled: the initial version contained 48 items and the subsequent version has 64 items (line drawings of familiar objects in both cases). Of the 25 cases with naming scores, \( N=13 \) and \( N=12 \) had done the 64-item and 48-item versions respectively (\( N=5 \) AD for each version). As reported in a previous publication,\(^{19}\) during the period of transition from use of the 48- to the 64-item version of this naming test, 13 patients with semantic dementia were given both versions in the same testing round to enable evaluation of the comparability of the two tests. The correlation between those patients’ scores on the two versions was nearly perfect (\( r=0.99 \)); it was therefore deemed safe to convert all scores to proportion correct and treat the two versions as equivalent. For present purposes, we wanted to compare naming error types as well as proportions correct. The errors were classified by a single observer (KP), blinded to pathological group, into the following categories: no response; circumlocutory semantic description (e.g. target: sledge; response: “slides down a hill”); single word semantic substitution (e.g. target: guitar; response: “violin”); phonological error (e.g. target: motorcycle; response: “myskikle”); incomplete word fragment (e.g. target: seahorse; response “horse”); and unclassifiable (e.g. target: pliers;
Pathological diagnosis (Fig. 1a): Brains were examined by the same senior neuropathologist (JHX) blind to the clinical information using histological and immunohistochemical methods detailed previously.[4, 5] AD pathology was diagnosed in cases reaching Braak stage 4 or greater, with presence of both neuritic plaques and neurofibrillary tangles, and with involvement of the isocortex (n=13). FTD-spectrum pathologies were diagnosed and divided into three subgroups according to immunohistochemical criteria. The first was a tau-positive group (FTD-T) that included classic Pick’s disease (n=3); corticobasal degeneration (CBD) (n=4); progressive supranuclear palsy (PSP) (n=4); and one with tangle only pathology and marked cell loss in BA 44/45 and 39. Second was FTD with ubiquitin-positive inclusions (FTD-U) (n=6); all were TAR DNA binding protein (TDP43) positive. One patient in the FTD-U group developed clinical motor neuron disease six years after symptom onset. The third group was tau-negative and ubiquitin-negative (dementia lacking distinctive histology, DLDH, n=2). Two of the 33 patients had mixed pathology: one FTD patient confirmed by tau-positive Pick bodies also showed minor, incidental AD changes; and one patient reaching the criterion for AD pathology also had early Parkinson’s pathology.

Results

Demographic characteristics (Table 1)
Although age at onset was 2.0 years older in the AD group, the degree of overlap between groups was high (Fig. 1b). Onset before 65 years occurred in 62% of patients with AD pathology (n=8) versus 45% of cases with FTD-spectrum pathology (n=9). Onset age before 60 years, however, occurred in seven (35%) of the FTD-spectrum group compared to only one (8%) with AD pathology. Onset before 60 years yielded specificity of 92% and a positive predictive value (PPV) of 88% for FTD-spectrum pathology although sensitivity for this was low (35%). The mean age at death in the AD pathology group was 73.4 (SD 7.4, range 63.8-85.5), 2.7 years older than that of the FTD-spectrum pathology group (mean 70.7, SD 8.8, range 52.0-84.9).

Table 1. Demographic characteristics according to pathology classification

<table>
<thead>
<tr>
<th></th>
<th>AD pathology</th>
<th>FTD-spectrum pathology</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M:F)</td>
<td>10:3</td>
<td>12:8</td>
<td></td>
</tr>
<tr>
<td>Age at onset (yrs)</td>
<td>65.55 (6.38),n=13</td>
<td>63.60 (7.76),n=20</td>
<td>0.44</td>
</tr>
<tr>
<td>Age at presentation (yrs)</td>
<td>67.75 (6.68),n=13</td>
<td>65.81 (7.68),n=20</td>
<td>0.45</td>
</tr>
<tr>
<td>Age at death (yrs)</td>
<td>73.41 (7.41),n=13</td>
<td>70.65 (8.75),n=20</td>
<td>0.34</td>
</tr>
<tr>
<td>Education (yrs)</td>
<td>11.58 (1.73),n=12</td>
<td>10.41 (1.46),n=17</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Values are expressed as means (standard deviations).

Kaplan-Meier survival curves are shown in Fig. 1c. Median survival in the AD pathology group was 8.1
years from symptom onset, and 6.3 years in the FTD-spectrum pathology group (P=0.81, log rank test). Dividing the FTD-spectrum group into tau-positive (n=12) and tau-negative (n=8), there was trend towards a difference favouring the tau-positive cases (median survival 7.8 years versus 4.0 years, P=0.10).

**Cognitive function** (Table 2)

62% of AD pathology patients and 80% of FTD-spectrum pathology patients had preserved global function within the first two years after onset, and this characteristic was only 38.5% specific and 80.0% sensitive for predicting FTD-spectrum pathology. The time duration from onset to ADL impairment was similar in the two groups as was performance of copy and recall of the Rey figure. With regard to the Rey figure, it was notable that each pathological group contained patients with both normal and severely impaired performance (Rey figure copy score range 2.5-35 in AD and 2-35 in FTD-spectrum; Rey figure delayed recall score range 0-18 in AD and 0-22.5 in FTD-spectrum). Importantly there was no difference in time from symptom onset to Rey figure testing that might have biased the results (AD group mean 3.00, FTD-spectrum group mean 3.49, P=0.63).

Table 2. Global function, ADLs and Rey figure scores according to the pathological classification.

<table>
<thead>
<tr>
<th>Features</th>
<th>AD pathology</th>
<th>FTD-spectrum pathology</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preserved global function</td>
<td>8,n=13</td>
<td>16,n=20</td>
<td>0.43</td>
</tr>
<tr>
<td>Time of intact ADLs (yrs)</td>
<td>4.64 (2.81),n=13</td>
<td>4.35 (2.72),n=20</td>
<td>0.77</td>
</tr>
<tr>
<td>Rey figure Copy (/36)</td>
<td>25.59 (11.05),n=11</td>
<td>28.89 (8.71),n=14</td>
<td>0.43</td>
</tr>
<tr>
<td>Rey figure Recall (/36)</td>
<td>8.36 (7.19),n=11</td>
<td>11.64 (6.92),n=14</td>
<td>0.26</td>
</tr>
</tbody>
</table>

ADLs =activities of daily living. Time of intact ADLs is the duration from disease onset to the first impairment of activities of daily living.

**Neuropsychiatric characteristics** (Table 3)

Emergence of a sweet food preference had the highest specificity (92.3%) for FTD-spectrum pathology, but sensitivity was very low (25.0%). The other most specific features for FTD-spectrum pathology were disinhibition (76.9% specific, 45.0% sensitive) and apathy (69.2% specific, 40.0% sensitive). Absence of depression was not useful in predicting FTD-spectrum pathology (sensitivity 55.0%, specificity 38.5%).

Table 3. Neuropsychiatric characteristics according to the pathological classification
<table>
<thead>
<tr>
<th>Feature</th>
<th>AD pathology</th>
<th>FTD-spectrum pathology</th>
<th>Specificity (%)</th>
<th>Sensitivity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweet food preference</td>
<td>1/13 (3)</td>
<td>5/20 (2.5-6)</td>
<td>92.3</td>
<td>25.0</td>
<td>83.3</td>
<td>44.4</td>
<td>0.36</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>3/13 (1.5-3.5)</td>
<td>9/20 (1.7-5)</td>
<td>76.9</td>
<td>45.0</td>
<td>75.0</td>
<td>47.6</td>
<td>0.28</td>
</tr>
<tr>
<td>Apathy</td>
<td>4/13 (2.5-8)</td>
<td>8/20 (1.5-10.5)</td>
<td>69.2</td>
<td>40.0</td>
<td>66.7</td>
<td>42.9</td>
<td>0.72</td>
</tr>
<tr>
<td>Absence of depression</td>
<td>8/13</td>
<td>11/20</td>
<td>38.5</td>
<td>55.0</td>
<td>57.8</td>
<td>35.7</td>
<td>1.00</td>
</tr>
</tbody>
</table>

PPV=positive prediction value, NPV=negative prediction value. Specificity, sensitivity, PPV and NPV are parameters for predicting FTD-spectrum pathology; scores in brackets indicate the time range (years) from symptom onset that these features emerged.

**Imaging features (Fig. 2)**

None of the six available scans from patients with AD pathology had disproportionate or asymmetrical frontotemporal atrophy (knife-edge atrophy), while this feature was evident in six of 15 in the FTD-spectrum pathology group. Therefore, knife-edge atrophy was 100% specific and 40.0% sensitive for FTD-spectrum pathology. The PPV and NPV of knife-edge atrophy for FTD-spectrum pathology were 100% and 40.0% respectively.

**Co-occurrence of features**

As the results indicated that (i) early age of onset, (ii) sweet food preference, (iii) disinhibition and (iv) knife-edge atrophy on structural imaging had the highest specificity (>70%) for FTD-spectrum pathology, a survey of prevalence of these symptoms was undertaken in the 15 FTD-spectrum patients who had had imaging. This revealed that 6/15 patients had one of these features; 6/15 had two features; 2/15 had three features; none had all four features. Only one FTD-spectrum patient had none of these features.

As less than half of the AD-pathology group had structural imaging available, the same survey could not be undertaken. Comparing the prevalence of features (i) - (iii) alone, the results were as follows: in FTD-spectrum pathology, 4/20 had no features; 11/20 had one feature; 5/20 had two features; none had all three features. In the AD pathology group, 10/13 (77%) had no features; 1/13 had one feature; 2/13 had two features; none had all three features.

**Naming (Table 4)**

The AD group made a significantly greater proportion of “don’t know” responses (P<0.001). The FTD-spectrum group made a significantly greater proportion of single word semantic substitutions (P=0.01). All other error rates were comparable between groups. Interestingly, none of the FTD-U patients made phonological errors in confrontation naming; excluding these, the proportions of patients
with FTD-T and AD that made phonological errors were similar: 6/9 versus 6/10 patients respectively.

Table 4. Confrontation naming as percentage of total with range in parentheses.

<table>
<thead>
<tr>
<th>Naming</th>
<th>FTD-spectrum</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall proportion correct</td>
<td>78% (14-95)</td>
<td>60% (23-88)</td>
</tr>
<tr>
<td>Error types:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Don’t know responses</td>
<td>8% (0-44)</td>
<td>36% (14-71)</td>
</tr>
<tr>
<td>Semantic descriptions (circumlocutions)</td>
<td>8% (0-33)</td>
<td>14% (0-73)</td>
</tr>
<tr>
<td>Single word semantic substitutions</td>
<td>50% (2-100)</td>
<td>22% (5-45)</td>
</tr>
<tr>
<td>Phonological errors</td>
<td>15% (0-84)*</td>
<td>17% (0-46)</td>
</tr>
<tr>
<td>Word Fragments</td>
<td>3% (0-20)</td>
<td>7% (0-33)</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>15% (0-50)</td>
<td>4% (0-13)</td>
</tr>
</tbody>
</table>

*Phonological errors were generated exclusively by the FTD-T subgroup.

**Discussion**

Grouping patients by pathology, four clinical features demonstrated specificity in predicting FTD-spectrum rather than AD pathology in patients presenting with PA: onset before 60 years, sweet food preference, disinhibition, and knife-edge fronto-temporal atrophy on structural neuroimaging. An examination of the combined prevalence of these features indicated that the majority of the FTD-spectrum group exhibited at least one feature whereas the majority of AD group had none. Neither early global cognitive impairment, poor non-verbal memory nor early impairment of self care was helpful in distinguishing AD pathology from FTD-spectrum pathology.

The AD pathology group was older than the FTD-spectrum group, consistent with the recognized consensus that FTD, on average, has an earlier onset than AD.\(^{[20, 21]}\) Although ‘early-onset’ dementia is typically defined as before 65 years and FTD is considered a major cause of early-onset dementia,\(^{[21, 22]}\) the present study indicated that this age was not a discriminating cut-off. About half of the patients in both groups had onset before 65 years. Onset before 60 years, however, had 92% specificity in predicting FTD-spectrum pathology in this series. At the other end of the age spectrum, onset beyond 65 years was not predictive of AD pathology; the oldest FTD-spectrum patient (FTD-U pathology) had symptom onset at 76.8 years.

The AD pathology group had a 1.8 year longer median survival, even though their mean age of onset was higher than the FTD-spectrum pathology group. Considering that advancing age is also a risk factor for death, this observation implies that PA patients with FTD-spectrum pathology progress faster, consistent with previous reports indicating that FTD is a more aggressive disease than AD.\(^{[23, 24]}\) In passing, it was noted that the FTD-spectrum PA patients with tau-positive inclusions had a significantly better prognosis than those with tau-negative pathology, a finding consistent with a previous report.\(^{[24]}\)
One might expect that AD pathology would be associated with a greater prevalence of early global cognitive decline as well as more deficits in non-linguistic cognitive domains such as memory and visuospatial ability. In fact, severe amnesia and visuospatial impairment have been regarded as exclusion criteria for FTLD according to the current consensus statement.[1] The present study, however, found no evidence to support a significant role of these deficits in discriminating between pathological groups. A substantial 62% of patients with AD pathology had preserved global function within the first two years following symptom onset. Measures of visuo-constructional ability and non-verbal memory from the Rey complex figure test yielded no significant differences between the two groups. Furthermore, although one cannot exclude the possibility that significant differences might have emerged with greater statistical power, it is unlikely that such a scenario would have any genuine clinical diagnostic utility because both groups in this series contained individuals with either normal or severely impaired performance on either measure. In recent studies, marked amnesia also presented as the dominant syndrome in 11% of pathologically confirmed FTD patients.[25, 26] This study confirms that, in the PA subgroup of FTD, the presence of anterograde amnesia cannot be regarded as a strict criterion to distinguish AD pathology from FTD-spectrum pathology; this resonates with a recent finding of comparable anterograde memory impairment in bvFTD and early AD suggesting that memory impairment might be a less desirable exclusion criterion for FTLD than previously thought.[27]

In contrast to those with early global decline, it was not possible to estimate whether there was a group difference in time to global cognitive impairment in those who had been intact at two years because many still had a relatively pure aphasia at their last clinic assessment. Anecdotally the most extreme examples were an AD pathology case and an FTD-spectrum case (PSP pathology) both with isolated language syndromes nine years and eight years, respectively, from symptom onset. In summary, although it has been proposed that the syndrome of “primary progressive aphasia” be reserved for patients with a relatively pure aphasia in, at least, the first two years of symptoms,[28] no evidence could be found in the current series to suggest that this rule conveys any meaningful distinction in pathological terms.

Time from onset to impairment of ADLs was also approximately equal between the two groups. Previous studies have reported that FTLD patients were more impaired than AD patients on basic ADLs.[23, 29] These studies, however, did not distinguish between the three subtypes of FTLD. A recent study of ADLs that divided FTLD into its three clinical subtypes and also included a clinical AD group matched for disease duration, reported that the bvFTD group was most affected whereas clinical PA and clinical AD were less severely impaired.[30] Taken together these studies suggest that bvFTD may be the subgroup that drives the apparent observation of FTLD as a condition that genuinely disrupts everyday functioning. The current findings additionally suggest that time to impairment of ADLs in PA is not dependent on pathological type.
Regarding neuropsychiatric features, sweet food preference and disinhibition were highly specific for FTD-spectrum pathology but with low sensitivity. These two features have been consistently reported to have value in distinguishing FTD from AD,\textsuperscript{[12, 31, 32]} and the present results indicate that these features have specificity with respect to this discrimination specifically within PA patients. Given that SD and bvFTD seem rarely to be associated with AD pathology,\textsuperscript{[2, 33]} the present results imply that sweet food preference and disinhibition are reasonably specific for all three variants of FTD once PA associated with AD pathology is excluded.

Knife-edge atrophy on structural imaging was 100\% specific for FTD-spectrum pathology but was only present in a minority of patients (sensitivity 40\%). Previous studies have reported that asymmetric frontotemporal atrophy was highly specific for FTD compared with AD or vascular dementia.\textsuperscript{[17, 18]} The present study confirms this finding for PA, but indicates that — whereas the presence of disproportionate frontotemporal atrophy strongly predicts FTD — its absence by no means rules out pathology in the FTD spectrum.

Although this retrospective study was motivated by a search for pathological predictors identifiable in the setting of a neurological assessment, confrontational naming data were available for about three-quarters of the patient sample. Perhaps unsurprisingly, the AD group was more anomic in terms of “don’t know” errors, possibly implying greater semantic involvement. That said, circumlocutions were comparable between groups, while single word substitutions (co-ordinate or super-ordinate) were more frequent in the FTD-spectrum group. Another interesting observation was that within the FTD-spectrum group, only those with FTD-T made phonological errors during confrontation naming. Although this could be interpreted as consistent with a previous study that reported apraxia of speech in FTD-T but not FTD-U,\textsuperscript{[34]} it was notable that the Alzheimer group had a comparable prevalence of phonological errors to that seen in FTD-T.

It is important to emphasize that the naming data can only be treated as a preliminary observation and that detailed analysis of linguistic function was not possible. Further prospective studies are necessary to test whether language profiles can reliably predict pathology. In particular, within the spectrum of PA, recent evidence suggests that a fluent anomic syndrome (logopenic aphasia) is predictive of Alzheimer pathology,\textsuperscript{[7]} while prominent motor speech disturbance (apraxia of speech) is predictive of the tauopathies: progressive supranuclear palsy and corticobasal degeneration.\textsuperscript{[35]} Data thus far, however, have been derived from relatively small case series. Prospective studies would be helpful to examine the predictive value of language features and, particularly, to evaluate PA cases that defy neat syndromic classification.

A final caveat with respect to the demographic information must be highlighted. This was not a population-based epidemiological study; patients were recruited from referrals to a neurology-led
cognitive disorders clinic. The clinic has some bias towards atypical dementia syndromes (such as PA) but there is quite possibly some additional bias towards younger-onset patients.

In conclusion, the present study highlights an emerging picture of clinical features that may help to discriminate PA patients with AD pathology from those with FTD-spectrum pathology (Table 4). Onset before 60 years, neuropsychiatric symptoms such as sweet food preference and disinhibition, and imaging features of knife-edge frontotemporal atrophy all show relative specificity for FTD-spectrum pathology. These can be added to the earlier finding that absence of posterior temporo-parietal lesions (using either FDG-PET or HMPAO-SPECT) was also highly specific for PA with FTD-spectrum pathology.\textsuperscript{[10]} While it is important to note that each of these features lacks sensitivity in isolation, it is rare for a PA patient with FTD-spectrum pathology to exhibit none of these features. In contrast it is common for all of these features to be absent in PA with AD pathology. Finally, the study highlights that impairment of global function within the first two years, poor memory and onset before 65 years are not useful in discriminating AD pathology from FTD-spectrum pathology.

Table 5. Clinical and imaging features with utility in distinguishing AD from FTD-spectrum pathology in PA (*predictive of AD pathology, all others predictive of FTD-spectrum pathology).

- Onset before 60 years
- Emergence of neuropsychiatric features associated with bvFTD (sweet food preference, disinhibition)
- Presence of knife-edge (including asymmetrical) frontal and/or temporal lobe atrophy
- Bilateral posterior temporo-parietal hypometabolism (PET) or hypoperfusion (SPECT)*
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LEGEND FOR FIGURES:

Figure 1a. Proportion of different pathology in clinically diagnosed PA patients. AD=Alzheimer’s disease; FTD-U=ubiquitin-positive FTD; DLDH=Dementia lacking distinctive histology; Tauopathies=tau-positive pathology; CBD=corticobasal degeneration; PSP=progressive supranuclear palsy; Pick=Pick’s disease. Figure 1b. Age of onset according to pathology classification. Figure 1c. Survival curves of the two pathology groups.

Figure 2. Structural imaging of three PA patients
A, B: Frontal and temporal imaging of one FTD-spectrum pathology PA patient, with asymmetrical frontal and/or temporal lobe atrophy.
C, D: Frontal and temporal imaging of one FTD-spectrum pathology PA patient, without asymmetrical frontal and/or temporal lobe atrophy.
E, F: Frontal and temporal imaging of one AD pathology PA patient, without asymmetrical frontal and/or temporal lobe atrophy.
Pathology distribution of PA patients

- AD (n=13) 40%
- Taupathies (n=12) 36%
- FTD-U (n=6) 18%
- DLDH (n=2) 6%
- CBD (n=4) 12%
- PSP (n=4) 12%
- Pick (n=3) 9%
- Tangle only dementia (n=1) 3%

Age of onset

Survival proportions