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Primary progressive aphasia: Diagnosis, varieties, evolution

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Abstract

A referred cohort of 67 clinically defined PPA patients were compared to 99 AD patients with formal language and nonverbal cognitive tests in a case control design. Language fluency was determined at the first and last follow up visits. Quantitation of sulcal and ventricular atrophy on MRI was carried out in 46 PPA and 53 AD patients. Most PPA patients (57%) are relatively fluent when first examined. Visuospatial and memory functions are initially preserved. Aphemic, stuttering, "pure motor" presentation, or agrammatic aphasia are seen less frequently. Later most PPAs become logopenic and nonfluent, even those with semantic aphasia (dementia). In contrast, AD patients were more fluent and had relatively lower comprehension, but better overall language performance. MRI showed significant left sided atrophy in most PPA patients. Subsequent to PPA, 25 patients developed behavioral manifestations of frontotemporal dementia and 15 the corticobasal degeneration syndrome, indicating the substantial clinical overlap of these conditions. Language testing, particularly fluency scores supported by neuroimaging are helpful differentiating PPA from AD. The fluent–nonfluent dichotomy in PPA is mostly stage related. The aphemic-logopenic-agrammatic and semantic distinction is useful, but the outcomes converge. (*JINS*, 2003, *9*, 710–719.)

Keywords: Primary progressive aphasia, Frontotemporal dementia, Pick complex, Alzheimer's disease

INTRODUCTION

Mesulam (1982) described a series of cases of slowly progressive aphasia and named the syndrome *primary progressive aphasia* (PPA; Mesulam, 1987). More than a century earlier, Arnold Pick's original case had progressive aphasia, in association with behavioral symptoms (Pick, 1892). In subsequent publications on Pick's disease (PiD), progressive aphasia was often the major symptom (Caron, 1934). We, among others, proposed that PPA was clinically and pathologically related to frontotemporal dementia (FTD) and PiD (Kertesz et al., 1994; Snowden et al., 1992). Although not emphasized in the original description of FTD, progressive language disorder is seen frequently with or without the behavioral abnormality and more recently a consensus was reached concerning its integration in the syndrome (Neary et al., 1998).

The initial presentation of PPA is usually word finding difficulty and later progressive loss of fluency with relatively preserved comprehension (Snowden et al., 1992; Weintraub et al., 1990). Alzheimer's disease (AD) patients have memory loss first, but may have word finding difficulty or aphasia when they are first referred, which poses a diagnostic dilemma (Appell et al., 1982; Cummings et al., 1985). The initial pattern of symptoms distinguishes the two groups of patients, but this may be difficult to establish with certainty. A period of two years of progressive aphasia with *relative* preservation of other functions and activities of daily living was suggested as the operational definition of PPA (Weintraub et al., 1990). Most published cases do not, however, provide consistent documentation for the 2-year criteria (Rogers & Alarcon, 1999; Westbury & Bub, 1997).

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The most typical clinical picture shows progression from anomic to a nonfluent type of aphasia. Some of these patients were described as logopenic when word finding difficulty was prominent, but phrase length was longer than four words and syntax was preserved (Weintraub et al., 1990). Decreasing speech output involves mainly spontaneous speech, while repetition is less affected (Karbe et al., 1993). At times the term transcortical motor aphasia was applied (Cappa et al., 1996). Patients are often divided into fluent and nonfluent types, but these terms are used casually without definition (Rogers & Alarcon, 1999). Individual case reports or small series showed a mixture of motor speech and linguistic disturbance, with few attempts at quantitation (Grossman et al., 1996; Thompson et al., 1997). There is a tendency to report only "nonfluent" cases under PPA, but even then, typical agrammatic Broca's aphasia is rarely described. Standardized language tests are not usually applied to compare populations of AD and PPA, although the BDAE subtests have been used in smaller subsets.

Articulatory difficulty, phonological paraphasias, stuttering, slow, dysprosodic speech, or verbal apraxia sometimes present as a distinct "aphemic" variety (Chapman et al., 1997; Broussolle et al., 1992; Cohen et al., 1993; Didic et al., 1998; Kertesz et al., 1994; Tyrell et al., 1991). These patients are less likely mistaken for having AD, however, the unexplained stuttering of adult onset is often considered "functional" or hysterical. Although a case has been made that this is a distinct entity which may remain isolated for years, (Chapman et al., 1997) there are no data showing how frequently this occurs, or what percentage of PPA patients actually have predominantly "aphemic" speech deficit.

A distinct form of progressive aphasia was described as "semantic dementia" by Snowden et al. (1989). These patients progressively lost the meaning of words, but retained fluency. Subsequent descriptions also adopted this term (Hodges et al., 1992). Patients with semantic dementia have a two-way disturbance of comprehension and naming, in addition to multimodality agnosia, and are arguably more aphasic than demented (Kertesz et al., 1998). Initially, articulation, phonology, syntax, and repetition remain intact, and this group of patients is often considered separately from PPA. Eventually, however, most of these patients also progress to a nonfluent state and often develop disturbances of behavior (Hodges et al., 1992; Snowden et al., 1989).

Mutism, considered characteristic of PiD, (Tissot et al., 1975) tends to be the end-stage of all forms of FTD and PPA, even for those starting with behavioral abnormalities rather than language disturbance. In PPA it may come relatively early, while the patient is still functioning in the community. Aphasia, logopenia, and mutism appear in the description of frontal lobe dementia (FLD) (Gustafson, 1987; Neary et al., 1988) and there is an extensive overlap among the variable descriptions of language deficit in FLD, FTD, and PPA. End-stage mutism also occurs in AD, but usually in hospitalized patients who already have a global dementia with loss of comprehension and basic functions of daily living (Appell et al., 1982).

This study aims to clarify diagnostic and clinical issues, in a referred population of PPA and AD patients. Our objectives are to examine the language characteristics of PPA in comparison to aphasia in AD, to assess the utility of clinical criteria and psychometric tests in diagnosis, to provide a clinically valid construct of the varieties of progressive aphasia, and to follow the course and outcome of PPA patients.

METHODS

Sixty-seven patients were diagnosed clinically as having PPA, on the basis of history and neurological examination, when the presenting symptom was a progressive language disorder, which remained predominant in comparison to other cognitive decline, such as memory and visuospatial function for at least two years using the definition of Weintraub et al. (1990). This was ascertained through clinical functional inquiry, including specific questions about the patient's memory, spatial orientation, using appliances, shopping, banking, and personal hygiene. We included a few patients with early symptoms of disinhibition and extrapyramidal symptoms because we consider these part of the syndrome. Patients with Parkinson's disease, Lewy body dementia, vascular dementia, or significant psychiatric disease were excluded on clinical grounds. All patients had neuroimaging to exclude neoplasm or other structural cause of dementia, in addition to blood work to rule out hypothyroidism, B12 deficiency, and other metabolic causes of dementia. The patients selected had detailed language examination with the Western Aphasia Battery (WAB; Kertesz, 1982) and most were able to carry out other cognitive tests detailed below. Some patients were referred with the diagnosis of AD or dementia (23), others with unspecified speech or language disorders (24), but 20 had already been diagnosed with PPA. One hundred and sixty-six patients with the diagnosis of AD, according to NINCDS-ADRADA criteria, had completed the WAB language examination as part of a cohort study. Ninety-nine of these were selected as controls on the basis of being examined at the same time of their illness as the PPA patients, based on the onset by history to the first examination (Table 1).

In some cases, the history of onset was in doubt and we suspected the forgetfulness, noted by the patient and the family, may have been word finding difficulty. On further observation of preserved orientation and activities of daily living, we would follow the patient as a *possible primary progressive aphasia*. However, we excluded 14 such patients with an indefinite onset. We also excluded 35 patients who had progressive aphasia after developing signs and symptoms of FTD and CBD.

Most patients, PPA population and AD controls, received yearly language and neuropsychological assessment while they were testable, some for as long as 8 years. Even longer clinical follow up was available in many patients, and 25

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Table 1. Demographics and aphasia quotients

		Sex M/F	Age	Months ill	AQ
PPA	$n = 67$	27/40*	66.7 ± 7.9**	38.0 ± 24.9*	68.1 ± 22.2***
AD	$n = 99$	40/59*	72.2 ± 7.5**	37.3 ± 21.4*	85.6 ± 11.7***

*Not significant. **$F(1,164) = 20.1$, $p < .000$ ***$F(1,164) = 43.5$, $p < .000$.

were followed until death. The yearly examinations were quantitated whenever possible, but here we detail only the initial diagnostic examination and some language tests, such as fluency, characteristics of speech output, and comprehension, on the last follow-up examination. The serial quantitation of language decline has been published in 10 patients (Karbe et al., 1993).

Neuroimaging with MRI or CT and SPECT was used to support the clinical diagnosis in all cases. Two neurologists, K.T. and A.K., knowing only that the patients had degenerative disease, rated right and left frontal, central, temporal, parietal, occipital, cortical and ventricular atrophy (altogether 20 items) for each MRI scans of 53 AD patients and 46 PPA patients on a scale of 0–3 (0 = *none*, 1 = *mild*, 2 = *moderate*, 3 = *severe*). The scores of left and right hemisphere regions were summed and compared with a ratio formula of (L − R)/(L + R). Two left-handed PPA patients with greater right atrophy were excluded.

RESULTS

Demographics

PPA patients were younger at onset, $M = 66.7$ (± 7.9) years, than AD patients, $M = 72.9$ (± 7.5), and the difference was statistically significant (Table 1). The duration of illness from onset to the first examination was the same, since patients in the two groups were matched in this variable. Average duration of PPA to death in 25 patients was 7.1 years ($SD = 3.2$, range 2–15). Mean duration of illness for PPA patients still alive was 7.0 years ($SD = 3$, range 2–15).

Quantitation of Language of PPA and AD Patients

Total language scores of the WAB or the aphasia quotient (AQ) was significantly worse in the PPA group at $M = 68.1$ (± 22.5) compared to AD [$M = 85.6 \pm 11.7$, $p \leq .001$; Table 1]. Significant differences between PPA and AD were present for all the language subtests, particularly language fluency (Table 2). Intragroup scores indicated comprehension subtests were not as impaired as fluency, naming and repetition in PPA, suggesting a pattern similar to nonfluent or Broca's aphasia. The intragroup comprehension/fluency ratio in the PPA group ($M = 1.35 \pm .71$) was significantly higher compared to AD [$M = 1.02 \pm .12$; $F(1,64) = 20.3$, $p < .000$]; comprehension/repetition in PPA ($M = 1.37 \pm .81$), *AD* [$M = 1.07 \pm .32$; $F(1,164) = 10.8$, $p < .001$]; comprehension/naming in PPA ($M = 1.48 \pm .67$), AD [$M = 1.17 \pm .24$, $F(1,164) = 17.5$, $p < .000$]. In the AD group, comprehension subtests were impaired relative to output fluency, similar to the pattern of sensory or Wernicke's aphasia. However, in milder cases the pattern was anomic aphasia in both groups. Reading, writing, calculation, and praxis were significantly more impaired in PPA (Table 3).

Table 2. Language subtest scores*

	Max. scores	PPA $n = 67$	AD $n = 99$	*P*-value
Spontaneous Speech Content	10	7.0 ± 2.7	8.2 ± 1.8	.001
Spontaneous Speech Fluency	10	6.5 ± 2.6	8.9 ± 1.1	.000
Comprehension Yes/No	60	51.4 ± 12.9	57.0 ± 4.2	.000
Word Recognition	60	52.4 ± 12.4	57.2 ± 5.9	.001
Sentence Comprehension	80	51.5 ± 23.2	66.3 ± 15.4	.000
Repetition	10	6.7 ± 2.7	8.7 ± 1.5	.000
Object Naming	60	41.5 ± 16.9	53.5 ± 9.0	.000
Word Fluency	20	5.6 ± 4.9	8.3 ± 4.9	.001
Sentence Completion	10	6.8 ± 3.6	9.0 ± 2.0	.000
Responsive Speech	10	6.6 ± 3.4	9.0 ± 2.3	.000

*Western Aphasia Battery

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Table 3. Reading, writing, praxis, calculation and nonverbal cognition†

	Maximum Scores	PPA	AD	*P*-value
Reading	100	69.0 ± 26.9 *n* = 61	81.0 ± 20.3 *n* = 90	.002
Writing	100	60.5 ± 34.0 *n* = 54	78.5 ± 22.6 *n* = 78	.000
Praxis	60	47.5 ± 12.3 *n* = 59	53.9 ± 6.0 *n* = 79	.000
Calculations	24	16.5 ± 8.6 *n* = 57	18.9 ± 5.8 *n* = 85	.05
Drawing	30	18.1 ± 8.0 *n* = 55	16.9 ± 6.0 *n* = 76	.304
RCPM*	35	19.7 ± 9.8 *n* = 57	16.0 ± 7.9 *n* = 80	.075
Block Design (shortened)	9	4.5 ± 3.6 *n* = 47	4.0 ± 3.2 *n* = 73	.358
Block Design (from WAIS)	19	9.3 (3.5) *n* = 23	6.8 (2.9) *n* = 57	.002
DRS**	144	95.7 ± 33.2 *n* = 38	97.6 ± 25.1 *n* = 84	.71
MMSE***	30	21.0 ± 7.1 *n* = 16	21.7 ± 7.3 *n* = 27	.70

†Unless indicated all tests are supplementary tests in the Western Aphasia Battery.
*Raven's Coloured Progressive Matrices.
**Mattis Dementia Rating Scale.
***Mini-Mental State Exam.

Nonverbal Tests and Discriminant Function Analysis of PPA and AD Patients

Nonverbal subtests such as Raven's Coloured Progressive Matrices (RCPM) were performed better by the PPA patients, in dissociation opposite to the language items. Block Design and the drawing subtest of the WAB were also better in PPA patients, significantly so in the Block Design (WAIS–R scores), but this did not reach significance in the shortened Block Design scores used in the WAB (Table 3). A stepwise discriminant function analysis for the five composite language and two nonverbal subtests of praxis and drawing of the WAB yielded Wilks's Lambda for fluency = 0.70, naming = 0.65, praxis = 0.61, drawing = 0.60 [λ = 0.59, *df* 4,116, $p < .000$]. This predicted the correct classification of 94% of the AD patients and 62.7% of the PPA patients ($x^2 = 59.3$, $p < .000$).

General Cognitive Screens

The Dementia Rating Scale (DRS) total score was not significantly different, indicating similar severity of the cognitive disorder in both populations (PPA: $n = 31$, $M = 96 \pm 34$; AD: $n = 50$, $M = 102 \pm 26$; Table 3). Executive functions, as measured by the Attention, and Initiation/Perseveration subtests of the DRS, were equally impaired in both PPA and AD. The dissociation of lower verbal and higher visuospatial and memory scores in PPA patients cancelled the differences in the total score. The Mini Mental State Examination (MMSE) was also the same in both groups, with greater variance in the PPA group (Table 3). The intersecting pentagon subtest, similar to other visuospatial tasks, was relatively preserved in PPA, but PPA patients do worse on the numerous language tasks of the MMSE.

Comprehensive Battery, including Memory Tests

A smaller subset of PPA ($n = 15$) and AD ($n = 42$) patients were able to carry out comprehensive memory and cognitive tests, despite the presence of aphasia (Table 4). Both Immediate and Delayed Recall of the Logical Memory scores from the WMS–R were significantly higher in PPA (Table 4). Similarly, the delayed recall of visual reproduction items, and RCPM, a visuospatial task, were better performed by the aphasic group constituting another feature of the double dissociation in the psychometric pattern. It is important to note that in this subset the language differences were still present, even though the patients were less severely affected. A step-wise discriminant function analysis of the language measures and the modified immediate and delayed verbal and visual reproduction memory subtests of the WMS–R yielded a Wilks's Lambda for fluency = 0.67, delayed visual reproduction = 0.52, naming = 0.39, delayed verbal memory = 0.39 (*df* 4,55, $\lambda = 0.37$, $p < .000$).

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Table 4. Patients with comprehensive testing

	PPA $N = 15$	AD $N = 42$	*P*-value
AQ*	79.7 ± 16.0	91.9 ± 6.1	.000
AGE	64.9 ± 7.9	71.1 ± 7.0	.005
Sentence Comprehension*	59.3 ± 20.4	72.0 ± 11.7	.005
Repetition*	82.1 ± 20.8	91.7 ± 8.4	.015
Object naming*	47.0 ± 15.2	58.0 ± 3.1	.000
Logical Memory Passage†	5.1 ± 4.4	3.0 ± 2.7	.029
Delayed Memory Passage†	3.7 ± 4.6	1.0 ± 1.7	.002
Immediate Visual Reprod.	12.3 ± 9.2	7.0 ± 5.3	.009
Delayed Visual Reprod.	5.5 ± 5.7	1.2 ± 2.1	.000
RCPM** (n =14 PPA, 36 AD)	24.7 ± 8.7	18.6 ± 7.3	.014

*Western Aphasia Battery. **Raven's Coloured Progressive Matrices. †First story of WMS–R.

This predicted the correct classification of 100% (42/42) of the AD patients and 73.3% (11/14) of the PPA patients (df 4,55, $x^2 = 53.0$, $p < .000$).

Language Fluency and the Course of PPA

Language fluency of conversational (spontaneous) speech was examined using the scoring criteria of the WAB. The WAB fluency score is a categorical rating from 0–10, incorporating multiple dimensions of speech, with severely nonfluent patients scoring 0–4. A fluency rating of 5 or 6 reflects significant degrees of logopenia, and scores of 8 and 9 with word finding difficulty and circumlocutions are considered fluent. The rating of 7 is reserved for jargon speech, also in the fluent category, and this was occasionally obtained in AD patients. Eleven PPA patients (16.4%) received severely nonfluent rating on the initial examination, 18 (26.8%) were significantly logopenic, and 38 (56.7%) were fluent (Figure 1). All AD patients were fluent, but 12 (12%) had sufficient word finding difficulty to be considered logopenic.

Since fluency could be stage-related, the results were analyzed in three groups of duration of the PPA. The patients seen early in the clinic within two years post-onset were compared with those seen at an intermediate time frame (3–4 years) and those seen late in the disease (over 4 years). Overall, fluency scores were significantly different on a Kruskal Wallis analysis of variance ($H = 16.7$, $p < .000$). However, early patients ($n = 26$) were not significantly different from the intermediate group ($n = 28$, Mann-Whitney $p < .41$). The early group $n = 26$ was significantly different from the combined ($n = 41$) intermediate and late groups ($p < .014$), and the intermediate ($n = 28$) time group was significantly different from the late group ($n = 13$, $p < .001$) and the combined early and intermediate group $n = 54$ was also substantially different from the late group $n = 13$ ($p < .000$).

Patients with PPA progressed to various degrees of dysfluency; 32 becoming severely nonfluent or mute with WAB fluency scores of 4 or below on their last follow up visit, 17 patients were significantly logopenic with a fluency rating of 5 or 6 in the WAB, 9 remained fluent and 9 was lost to follow-up (Figure 1). The average duration of the follow up visit was 3.2 ($SD = 2.4$) years. Eight initially fluent patients stayed fluent (average follow-up $M = 2.25$ years, range 1–5 years); 14 fluent patients became logopenic ($M =$ 3.3 years, range 1–6 years); 12 fluent patients became nonfluent ($M = 4.3$ years, 1–9 years), and 4 patients had no follow-up. Four logopenic patients stayed the same ($M =$ 1.75 years, range 1–4 years); 13 logopenic patients became nonfluent ($M = 2.38$ years, range 1–5 years), and 1 had no follow-up. The total language scores (AQ) of the PPA patients declined considerably more on yearly examinations than the AD patients. PPA patients ($n = 38$) had on average decline of AQ/year of 12.0 (± 15.3) compared to the 4.7 (± 8.3) for the AD patients ($n = 55$). In a repeated measures general linear model this interaction of Time (1 year between tests) × Group was significant [$F(1,91) = 8.87$, $p < .004$].

Clinical Categories of PPA on Presentation

Those PPA patients ($n = 38$) who had video recording of their speech at the first examination were further distinguished by rating the clinical characteristics of their speech and language disorder by three independent raters. These varieties were defined clinically according to current descriptions; and 2/3 agreement was chosen as final:

1. Anomic: word finding difficulty with only mildly impaired or normal fluency and rate of output, $n = 17$; average time from onset: 2.8 (SD: 1.9) years.

2. Logopenic: significant word finding difficulty and moderate to severe decrease of output, with relatively preserved syntax, phonology and articulation, (Weintraub et al., 1990), $n = 7$; time from onset $M = 4.2$ (SD: 4.0) years.

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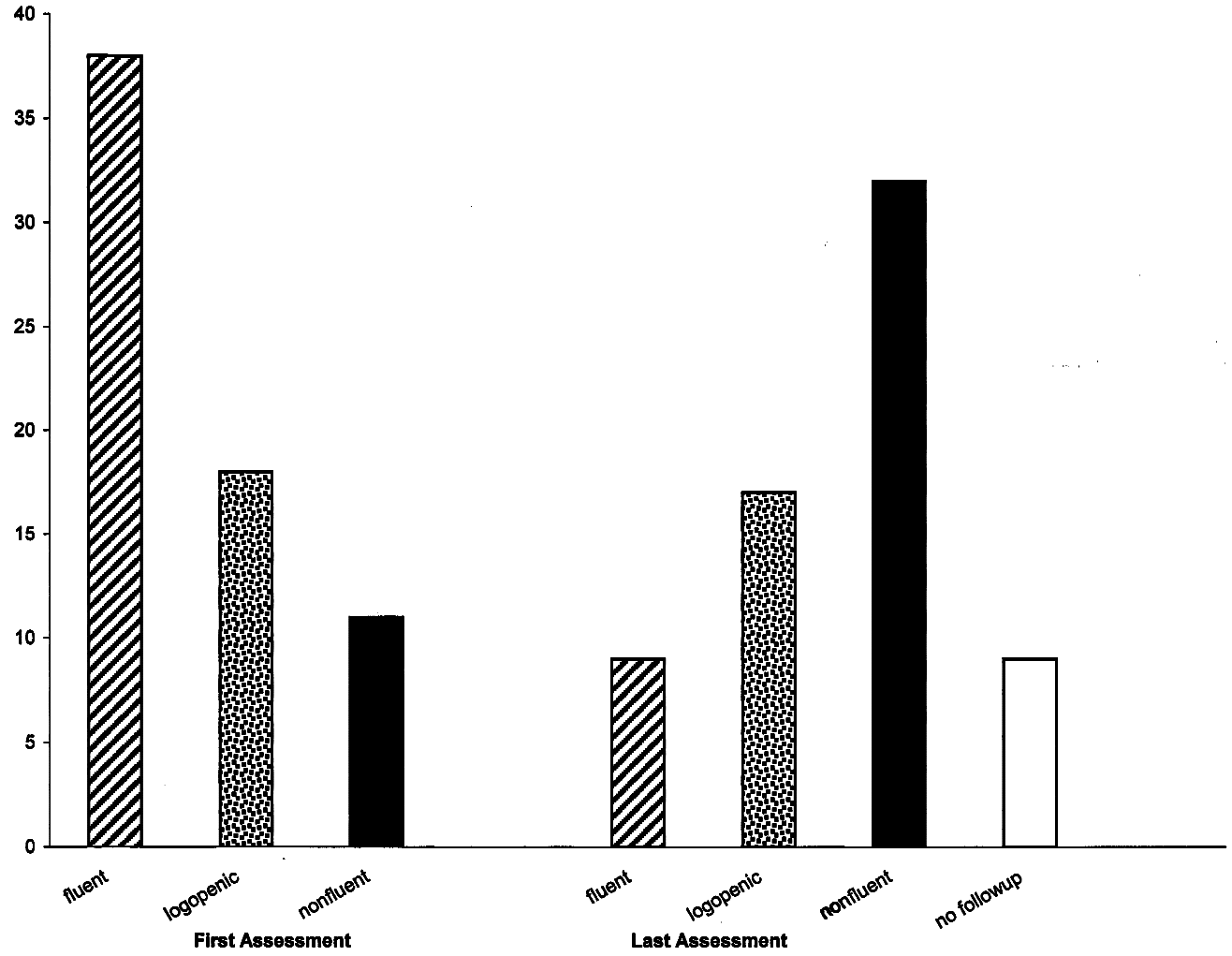

Fig. 1. The distribution of fluent logopenic and nonfluent aphasia at the first and last assessment.

3. Aphemic variety, predominantly phonological, articulatory errors and stuttering or verbal apraxia, (Cohen et al., 1993), $n = 6$; time from onset $M = 3.6$ (*SD*: 2.8) years.
4. Nonfluent aphasia with definite agrammatism, in addition to phonological, articulatory errors and anomia (Broca's aphasia; Goodglass & Kaplan, 1972), $n = 4$; time from onset $M = 1.75$ (*SD*: 1.5) years.
5. Semantic aphasia (dementia) where the meaning of words is lost while fluency, syntax and phonology remain relatively unimpaired, (Snowden et al., 1989), $n = 2$; time from onset 1 and 4 years.
6. Mute when patients were first seen but still ambulant and cooperative with testing, showing relatively good comprehension, $n = 2$; both seen at 3 years from onset.

Neuroimaging

The sum of the right hemisphere atrophy scores were subtracted from the left and this asymmetry score was compared between the PPA and AD groups with ANOVA. The PPA group had significantly greater left sided atrophy than the AD group [$M = 5.5$ (4.0) for the PPA patients and $M = 1.3$ (2.4) for the AD patients; $F(1.97) = 42.0$, $p < .000$]. When ratio measures of $(L - R)/(L + R)$ were used, comparing the asymmetry to the total atrophy, the PPA group still showed significantly greater left sided atrophy [PPA = 0.37 (0.29), AD = 0.17 (0.28); $F(1,97) = 11.56$ $p < .001$].

Based on the atrophy ratings of 0–4 for sulci and ventricles, if the left sided score was 3 or greater than the right, the scan was classified as focal, otherwise it was considered symmetrical. Forty-two of 46 PPA scans (91%) were focal and 46 of the 53 AD scans (87%) were symmetrical (correctly classified) (associated white matter lesions were mild to moderate and were not considered in the atrophy ratings).

PPA and Associated Syndromes

Twenty-five patients developed the behavioural symptoms of FTD conforming to the Lund Manchester criteria (Neary et al., 1998) secondary to PPA. Fifteen patients with PPA subsequently developed the extrapyramidal–apractic syn-

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drome of corticobasal degeneration (CBDs; Kertesz et al., 2000). Eight PPA patients had both behavioral symptoms (FTD) and the CBD syndrome. The time of onset for the secondary and tertiary syndromes was variable in a range of 0–8 years, $M = 4.6$, $SD = 2.8$. In 4 cases PPA, FTD and CBD symptoms followed the onset of PPA closely. In 2 cases additional motor neuron disease (MND) was documented.

DISCUSSION:

Previous clinical studies of PPA with neuropsychological data have been either single case studies, small series of patients, (Cappa et al., 1996; Grossman et al., 1996; Karbe et al., 1993; Thompson et al., 1997; Weintraub et al. 1990) or literature reviews, combining material from various centers with differing methods of observation and few data points in common (Rogers & Alarcon, 1999; Westbury & Bub, 1997; Zakzanis, 1999). They often focused on neuroimaging (Chawluk et al, 1986), occasionally on neuropathology (Kertesz et al., 1994). Patients were examined at different stages, which contributes to the clinical heterogeneity. Our population of progressive aphasics received a uniform set of language tests and annual follow up with neuropsychological testing and neuroimaging when possible.

This study tries to address particularly the diagnostic issue of PPA vs. the language deficit in AD. Patients with AD presenting with memory loss often develop a language disorder later, but this is milder, anomic or paraphasic (Wernicke's type) with comprehension deficit (Appell et al., 1982; Cummings et al., 1985; Faber-Langendoen et al., 1988). On the other hand, patients with probable PPA have a history of primary language impairment, which progresses to a definite aphasia, characterized by word finding difficulty, decreased fluency, and significantly lower language scores, but without significant loss in other cognitive domains over 2 years. This time interval, sometimes established by history rather than direct observation, conformed to the operational criteria of Weintraub et al. (1990). The 2-year primacy is relative, since there were patients who developed the behavioral disorder of FTD shortly after onset. Some of the patients seen later have cognitive deficit in other domains caused by the language impairment. A standardized aphasia test, such as the WAB, is helpful to show that in PPA patients the scores are definitely in the aphasic range, while AD patients are nearer to normal. Isolated naming or word fluency tasks are less specific. Comprehension showed early impairment with AD patients, and relatively less impairment in the PPA patients compared to their fluency. The spontaneous speech of AD patients may be circumlocutory, even confabulatory because they lack content, or they may not understand all questions. Word finding difficulty is more evident in early PPA, but what speech they have tends to be more relevant.

The fluent/nonfluent distinction, although frequently referred to, does not appear consistent or reliable in the literature on PPA. Case studies emphasizing the fluency–nonfluency distinction have been confounded by the problem of examining patients at different stages of their illness. Most of our cases were fluent initially, but increasing word finding difficulty eventually rendered them logopenic and nonfluent. To add to the staging problem, the definition of fluency varies from centre to centre and reviews of the literature of cross-sectional case reports are misleading in categorizing this dimension (Rogers & Alarcon, 1999). Nevertheless, quantitation of fluency in our larger series was the best discriminant function overall, in distinguishing PPA from AD. Table 5 summarizes the diagnostic comparison.

Table 5. Diagnostic comparison of PPA and AD

	PPA	AD
Language at presentation	impaired	intact
Early, 0–3 years from onset	anomic	anomic
	logopenic	fluent
Midstage, 3–6 years from onset	logopenic	fluent
	Broca's***	Wernicke's****
Late stage	mute	irrelevant, jargon
Comprehension	preserved	impaired
Memory early	preserved	impaired
Visuospatial function*	preserved	impaired
ADL** early	preserved	impaired

*Recommend intersecting pentagons.
**Activities of Daily Living.
***Nonfluent, agrammatic, phonologically impaired.
****Fluent paraphasic speech, poor comprehension.

Logopenic patients have significant word finding difficulty, decreased overall fluency and rate of speech, yet articulation and phonology are relatively preserved. The aphemic variety is distinct even in the early fluent phase because of the stuttering and phonological errors, sometimes associated with dysarthria and dysphonia. It evolves from relative fluency to nonfluent speech as word finding difficulty increases. The aphemic variety tends to have more frontal involvement on neuroimaging (Tyrell et al., 1991). The initial distinction has been striking enough to consider these patients as having different diseases (Mesulam, 2001). However, we have seen both progress to a more severe nonfluent aphasic and finally mute state as a rule. We have not seen isolated dysarthria without eventual language impairment, except in motor neuron disease.

The agrammatic variety of nonfluent progressive aphasia is similar to Broca's aphasia due to a stroke. The combination of agrammatism, verbal apraxia and phonological errors, relatively infrequent at onset, is seen later in the middle stage of the illness. It may be missed as the patient declines because with further decrease in fluency, agrammatism becomes difficult to distinguish. Some have attempted to study grammaticality by indirect tasks, such as comprehension of grammatically complex sentences, bypassing speech output (Grossman et al., 1996). In many cases, however, logopenia seems to progress to mutism without definite agrammatism.

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Wernicke's aphasia with phonological or neologistc jargon is observed in mid-stage AD (Appell et al., 1982), but not in PPA. There is a certain amount of convergence because some of the AD patients will develop decreased fluency and output. However, they retain their semantic confusion and paraphasic responses even when they become less fluent. Another classification of progressive aphasia included a "mixed" group with comprehensive deficit which was considered more likely to have AD pathology (Snowden et al., 1992).

Semantic aphasia or semantic dementia may not have much, if any abnormality of speech output, and the diagnosis is made by the combination of a multimodal naming and comprehension deficit. Families report the loss of meaning for words or things perceived, providing the first clue for the diagnosis, and the most striking feature on examination in the loss of comprehension for common words, while conversation fluency, repetition, and memory are preserved. Initially, a clinical pattern of semantic aphasia is similar to AD language impairment, and only the presence of multimodal loss of semantic field is sufficiently distinct to classify this group separately. Eventually increasing logopenia and mutism develops. We included them in this study because they have clinical and biological features common with PPA. Furthermore, in the majority of cases these patients develop a behavioural abnormality which is characteristic of FTD. We did not include cases of semantic aphasia which appeared secondary to FTD, a relatively more frequent association, which also suggest the overlap of these conditions.

The double dissociation of verbal and nonverbal cognitive tests between PPA and AD was best demonstrated in a smaller group of patients, who presented earlier and were able to participate in comprehensive testing (Table 4). Later, visuospatial and performance tasks were impaired in both groups, often because of impaired executive function, or inattention. Aphasic patients had apraxia, impairing test performance on several cognitive tasks. Drawings were generally better performed in early PPA patients, but deteriorated in later stages of the illness. Both PPA and AD patients had difficulty with calculation, possibly because different functions, such as short-term memory, spatial processing, and the language component required for arithmetic, were affected by different pathologies.

Generalized dementia screens, such as the DRS, were equally impaired in the two groups because the language performance and executive deficits measured by the subtests, although affected differentially, seemed to balance each other in the total score (Table 4). Previous reviews also found dementia screening insensitive to the differential diagnoses of AD, FTD, and PPA (Zakzanis, 1999). The use of MMSE in PPA can be misleading because it classifies PPA patients as demented, even though their deficit is mainly in the language domain. The MMSE is weighted for language items and PPA patients perform poorly on word recall, even though they may have well preserved orientation. Since the MMSE is widely used to classify patients in treatment trials this may have resulted in the inclusion of many PPA patients inappropriately. Nevertheless, using the MMSE may alert the clinician to the diagnosis of PPA when orientation and drawing is preserved, in contrast to a disproportionate impairment of the language items.

Apraxia, frequently associated with PPA is sometimes prominent enough that cases are described as primary progressive apraxia with the aphasic component mentioned as a secondary feature. In our cases, the overall apraxia scores were significantly worse in PPA than in AD. The type of apraxia ranged from limb kinetic and ideomotor to ideational. At times orofacial apraxia is emphasized especially in the aphemic variety. In stroke, apraxia is usually ideomotor and limb-kinetic, associated with left hemispheric lesions, while ideational apraxia is seen only if large or bilateral lesions are present. However, in degenerative disease producing the clinical syndromes of PPA and CBDs, ideational apraxia, defined as object use apraxia, can be prominent and out of proportion to other varieties of apraxia (Kertesz et al., 2000). Variable amounts of extended praxis testing were carried out beyond the WAB subtests and the quantitation of object use apraxia is a subject of another study.

Measures of atrophy provide supportive data that neuroimaging plays an important adjunct role in the diagnosis. Most of our patients had MRI or CT and SPECT, and so far MRI appears the most useful in the differential diagnosis. Significant left frontotemporal atrophy is seen in most PPA patients, but there were a few exceptions to this rule. In early stages, the lack of neuroimaging confirmation of focal atrophy should not preclude the diagnosis of PPA. In later stages more bilateral or diffuse atrophy may supervene. Further quantification of the atrophy has been carried out in some of these patients, and the results were published elsewhere (Fukui & Kertesz, 2000). Arguably the clinical definition of the disease should be independent from neuroimaging, although several small series of PPA and FTD are selected on the basis of neuroimaging abnormality (Edwards-Lee et al., 1997). The occasional meningioma or vascular malformation underlying slowly progressive aphasia indicates the necessity of carrying out some form of neuroimaging in all cases.

The development of secondary and tertiary syndromes of CBDs and FTD suggests a significant overlap between PPA and these entities. The behavioural symptoms of FTD may be overlooked when aphasia is severe, or considered as part of "global dementia." The secondary occurrence of progressive aphasia in FTD and CBDs is the corollary of this overlap. We did not include these patients in this study in order to keep the focus on PPA. Associated motor neuron disease (MND) was infrequent, occurring in two cases. On the other hand, swallowing difficulty developed in many patients as a terminal feature. The exact proportion of bulbar MND could not be determined as these patients were not available for detailed investigation, such as electromyography.

We proposed that PPA is not just a symptom of heterogenous pathologies as it is sometimes claimed, but a syn-

drome most commonly associated with an overlapping clinicopathological pattern which we called the "Pick complex" (Kertesz et al., 1994). At times, focal AD has been described with the syndrome (Galton et al., 2000; Karbe et al., 1993; Mesulam, 2001). One of our cases previously published as PPA with AD pathology fell in the category of "possible PPA" because of doubtful early history (Karbe et al., 1993). Nevertheless, investigators describing PPA in depth believe it is distinct clinically and biologically from AD (Mesulam, 2001). Too much emphasis on heterogeneity obscures the importance and hinders the recognition of this syndrome as a relatively frequent and distinct component of PiD/FTD. Although clinical and pathological definitions vary from series to series, when the clinical syndrome of PPA is seen, there is a high probability that Pick complex pathology will be the underlying condition (Kertesz & Munoz, 1998; Mesulam, 2001). All 10 of our probable PPA cases that came to the autopsy had Pick complex pathology: 3 Pick's disease, 4 CBD, and 3 with tau and synuclein negative ubiquitinated (MND) inclusions (Kertesz & Munoz, 2003). Recent description of the clinical phenotypes of familial FTD linked to chromosome 17, some with tau mutations, some lacking tau histopathology, revealed a significant number of progressive aphasias (Bird et al., 1999; Zhukareva et al., 2001) providing a strong genetic confirmation of the nosologic position of PPA in frontotemporal lobar degeneration.

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