Profiles of Language Impairment in Primary Progressive Aphasia

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• *Objective.*—The profile of language impairment in patients with primary progressive aphasia in comparison with the language impairment in patients with Alzheimer's disease and after stroke.

Design.—The Western Aphasia Battery and the Mattis Dementia Rating Scale evaluated the language and cognitive impairment. Follow-up studies were done 1 to 5 years after the initial testing in seven of 10 patients with primary progressive aphasia, and a postmortem examination of the brain was done in two patients.

Setting.—All 10 patients with primary progressive aphasia were previously healthy, community-dwelling persons when first tested.

Patients and Other Participants.—All patients with primary progressive aphasia reported at least a 2-year history of slowly progressive aphasia without other signs of global dementia. The initial Western Aphasia Battery results of the 10 patients with primary progressive aphasia were compared with those of a sample of 10 patients with probable Alzheimer's disease and with those of a sample of 10

In 1982, Mesulam¹ presented a study of six patients who experienced slowly progressive language disorder without additional intellectual and behavioral disturbances of dementia. The clinical features of primary progressive aphasia (PPA) without dementia were different from those of other degenerative brain disorders, eg, Alzheimer's disease (AD). Aphasia typically started in presenium, ie, before 65 years of age. Speech fluency and naming skills were most often affected.^{2,3} The course of the disease was relatively benign. Aphasia was slowly progressive, while nonverbal cognitive functions were preserved for several years. Based on neuroradiological findings and on a cortical biopsy specimen in one case, Mesulam argued that a focal cerebral degeneration predominantly of the left perisylvian region may have caused the clinical syndrome.

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patients with aphasia due to a left hemispheric stroke. Both reference samples were matched for age and sex; the sample with stroke-caused aphasia was additionally matched for the aphasia type.

Results.—Expressive language disability with reduced speech fluency and anomia but preserved language comprehension and nonverbal cognition were typical features in early stages of primary progressive aphasia. Spontaneous speech was significantly more impaired in patients with primary progressive aphasia in comparison with those with aphasia after left hemisphere stroke and with language impairment in patients with Alzheimer's disease. Follow-up examinations revealed continuous, often rapid deterioration of language impairment. The neuropathological examination showed Alzheimer's disease in one patient and Pick's disease in the other.

Conclusion.—The profile of aphasia suggests that primary progressive aphasia tends to affect anterior parts of the language-dominant cortex first.

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Although previous studies had already described progressive aphasia without generalized dementia,^{4,5} the increasing interest in degenerative cerebral disease and especially in focal dementia has stimulated more detailed investigations of PPA in the last decade. These PPA studies, however, showed quite a heterogeneity of clinical features. They found that PPA was also likely to occur in senium, ie, after age 65 years,⁶⁻⁹ and it was sometimes a precursor of global dementia when the patients were followed up longitudinally.^{9,10} In early stages of PPA, patients frequently presented with anomia^{1,6,7,10-12} and with reduced speech fluency^{1,6,9,13,14}; but there were also some patients who had fluent speech,^{1,7,15-18} with predominantly reduced comprehension^{1,9,10} or poor repetition.^{1,8} Thus, some questions about the clinical features of PPA remained controversial. Is PPA a degenerative disorder restricted to only one cognitive domain or is it a precursor of global dementia? Are type and profile of the language disorder in PPA different from those of aphasia of other origin, and more specifically, what are the differences between PPA and aphasia in AD?

Pathological examinations of postmortem brains showed a variety of underlying disease in PPA. Kirshner et al¹⁹ studied two patients with PPA who died 2 and 10 years after the onset of aphasia. Postmortem examination

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Table 1.—Clinical Data of Patients With PPA*						
Patient No./Sex/Age at Onset, y	First and Last WAB, Years From Onset	First and Last AQ	Global Dementia, Years From Onset	Present Age, y		
1/M/81	2	68.2	3	Died at 85		
2/M/55	2	80.0	3	Died at 58		
3/F/71	5-6	84.8-73.9	6	78		
4/F/62	2-4	72.0-27.6	7	70		
5/M/75	2	69.6		77		
6/M/77	2-7	92.6-32.5	7	89		
7/M/76	2-5	78.9-21.2	3	83		
8/F/80	2-3	82.6-72.2	4	85		
9/M/65	3-4	70.8-53.8		70		
10/M/61	1-3	86.5-42.3	4	66		

*PPA indicates primary progressive aphasia; WAB, Western Aphasia Battery; and AQ, Aphasia Quotient.

of the brain showed focal spongiform changes in the left frontal and temporal cortex, which were distinct from other central nervous system degenerative diseases. Other investigators, however, found PPA associated with Pick's disease,^{17,20} AD,^{16,18,21} Creutzfeldt-Jakob disease,¹⁵ and focal neuronal achromasia.¹³

We analyzed the language impairment in 10 patients who initially presented with the clinical syndrome of PPA. We compared the profile of language impairment in early PPA with the language profiles in early AD and in aphasia due to left middle cerebral artery ischemic strokes. Follow-up studies in seven of 10 patients provided longitudinal information. Neuroimaging techniques (magnetic resonance imaging [MRI], cranial computed tomography) were used to investigate in vivo local or global changes in the brain tissue. Autopsy findings in two cases elicited the underlying brain abnormality.

SUBJECTS AND METHODS

The study included 10 patients (seven men, three women, all right-handed; mean [±SD] age at first examination, 72.6±8.4 years) (Table 1). Primary progressive aphasia was diagnosed according to the following criteria: All patients were previously healthy community-dwelling subjects who had experienced an insidious onset of aphasia with gradual progression in the absence of other signs of global dementia. Despite their gradual deterioration in verbal communicative skills, all patients were still able to cope with all activities of daily living, such as banking, driving, or gardening, when they were first examined. Some continued to play bridge or golf fairly well, and some still traveled alone, sometimes even abroad, eg, to Europe. No patient presented with a history that suggested other neurological disorders, especially not stroke or vascular dementia.²² The patients were first examined on average 2.3 years (range, 1 to 5 years) after the onset of symptoms (Table 1). Seven patients were reexamined 1 to 3 years after the first examination. This group includes patient 10, who was initially tested 1 year after the onset of symptoms. Also on the second test, clinical findings in patient 10 were commensurate with the diagnosis of PPA so that at least a 2-year history of PPA was available in all patients. In all cases, the neurological examination revealed no pathological findings except for the language disorder.

Brain structure was studied in eight patients using MRI (cases 2, 3, and 5 through 10) and using cranial computed tomography in one patient (case 4). Figure 1 shows MRI scans of one patient (case 5). Two patients (cases 1 and 2, Table 1) died before the present study was completed. Autopsy was done in both cases. Histopathological examination of serial coronal sections through both hemispheres and transverse sections through the brain stem

and cerebellum included samples of frontal, temporal, parietal, and occipital cortical areas and of several other regions of interest (eg, basal ganglia, thalamus, hypothalamus, hippocampus).

Standardized tests investigated the neuropsychological impairment in all patients. The Western Aphasia Battery (WAB)²³ was used to evaluate the degree of language impairment. Additionally, the Dementia Rating Scale (DRS)²⁴ gave information about the general decline of cognitive skills. Retests in seven patients that were done one or several times 1 to 5 years after the first assessment (Table 1 and Fig 2) added some longitudinal information.

The initial WAB scores of the patients with PPA were compared with an age- and sex-matched sample of patients with AD and of patients with aphasia due to left middle cerebral artery stroke. The comparison was done to investigate differences of aphasia profiles between PPA and aphasia in AD and after stroke. Both reference groups had equivalent premorbid education and were free of any other neurological, psychiatric, and medical disorder that could influence cognition or language. The AD reference group was taken from a sample of 112 patients who met the cri-teria for probable AD.²⁵ The AD reference sample comprised 10 patients (seven men, three women; mean age, 72.3±8.8 years) who reported, on average, a 2.3-year (range, 1- to 7-year) history of mental deterioration when first admitted and tested with a neuropsychological test battery that included the WAB. Reference patients with stroke-caused aphasia were taken from a group of 398 patients with aphasia after a single stroke in the territory of the left middle cerebral artery. The stroke patients were also matched according to the aphasia type to improve the comparability of aphasia profiles. The stroke reference group included 10 patients (seven men, three women; mean age, 73.0±8.0 years) who had had a stroke between 3 and 12 weeks before they were tested. In the PPA group and in the group with stroke-caused aphasia, nine patients had anomic aphasia and one had conduction aphasia.

The statistical analysis compared the mean WAB scores among the three groups. One-way analyses of variance (ANOVAs) were calculated with Tukey's post hoc comparisons. Initially, a one-way ANOVA was performed to compare the Aphasia Quotient (AQ) of the three groups to evaluate any general difference in the degree of language impairment. In a second step, four one-way ANOVAs compared the subtotals of the language subtests of the WAB (spontaneous speech, comprehension, repetition, naming) among the three subject groups. The results of all individual WAB subtests, including the verbal subtests (information content, fluency, yes-no questions, auditory word recognition, object naming, word fluency, sentence completion, responsive speech), reading, writing, praxis, and construction items (drawing, block design, calculation, Raven's Coloured Progressive Matrices [RCPM] score), were finally compared. To control for the increased probability

	Table 2.—Data of	Initial WAB and Its Sub	otests*	
Subtest	Maximum Score	PPA, Mean±SD	Stroke, Mean±SD	AD, Mean±SD
Age, y		72.6±8.4	73.0±8.0	72.3±8.8
Aphasia Quotient	100	79.6±7.9	87.2±8.9	91.0±5.4†
Spontaneous speech	20	14.6 ± 2.4	16.9±1.7‡	18.5±1.6‡
Information content	10	7.6±1.3	8.3±0.9	9.3±0.9§
Fluency	10	7.0 ± 1.8	8.6±1.1	9.2±0.9
Comprehension	10	8.4±0.8	9.2±1.0	9.4±0.7
Yes/no questions	60	57.6 ± 3.9	58.8 ± 2.1	57.2 ± 2.7
Auditory word recognition	60	57.6 ± 3.8	57.9 ± 3.1	59.2 ± 1.0
Sequential commands	80	53.4 ± 11.6	67.9 ± 17.4	70.8±12.9
Repetition	10	8.0 ± 1.4	8.7±1.1	9.4 ± 0.5
Naming	10	7.3±1.6	8.5 ± 0.9	8.6±0.5
Object naming	60	49.2 ± 10.3	56.4 ± 3.0 ¶	57.8±2.1¶
Word fluency	20	5.9 ± 4.1	10.2 ± 5.1	9.0 ± 2.7
Sentence completion	10	9.2 ± 1.6	8.9 ± 1.9	9.6±0.8
Responsive speech	10	9.1±1.3	9.4±1.3	9.8±0.6
Reading	100	83.2±14.3	75.1 ± 20.5	86.8±7.6
Writing	100	71.7±23.9	52.9 ± 27.3	80.5 ± 8.9
Praxis	60	47.5±12.6	56.8 ± 4.1	55.8 ± 2.0
Drawing	30	16.2 ± 6.7	15.3 ± 4.1	15.7±2.3
Block design	9	5.7 ± 2.1	5.4 ± 3.1	3.5 ± 2.3
Calculation	24	20.8 ± 3.9	17.0±8.1	19.6±4.8
Raven's score	37	19.9 ± 7.1	22.5 ± 4.5	14.5 ± 5.8

*WAB indicates Western Aphasia Battery; PPA, primary progressive aphasia; and AD, Alzheimer's disease. Probability was calculated by one-way analysis of variance, Tukey's post hoc comparison (values are comparison with group with PPA). Significance level was <.01. Unless otherwise indicated, the performance in all other subtests was not significant.

+P=.007 between PPA and reference group.

P=.0004 between PPA and reference group.

§P=.006 between PPA and reference group.

||P=.0024 between PPA and reference group.

¶ P=.01 between PPA and reference group.

of type I errors when doing multiple one-way ANOVAs, we reduced the accepted level of significance to P=.01.

REPORT OF PATIENTS

PATIENT 5.—A 78-year-old retired sales manager reported an approximate 2-year history of slowly progressive language deterioration. He seemed withdrawn, and his wife noticed that he spoke much less than previously. He still coped with all activities of daily living, drove his own car, did his banking. He still enjoyed reading books. He was able to remember dates, and his remote memory was completely intact. He continued to play bridge quite well. On examination, he looked well for his age; there were no pathological neurological findings except for his communicative disorder. His speech fluency was generally reduced to short sentences with poor grammatical structure or phrases consisting of single words with long pauses between. He had at times fluent utterances, especially automatic sentences. He had word-finding difficulty; sometimes he used phonemic paraphasias, but most often he was mute, not uttering any word. His language understanding was much better, which was especially obvious when he responded correctly to multiple-choice questions. He was fully oriented and cooperative and easily recalled recent and remote events. He still lives with his family.

PATIENT 6.—This 79-year-old retired draftsman and music teacher was admitted to the urology service because of benign prostatic hypertrophy. When the history was taken, he reported that he had experienced gradually progressive word-finding difficulty and some hesitation in his speech for about 2 years. His wife noticed that he had some difficulty "in expressing himself." But since he was not really disabled at that time, he had never gone to a physician because of his language disorder. On exam-

ination, he was fully oriented and was pleasant and cooperative. His memory for recent and remote events was well preserved. His speech was slightly hesitant, with some word-finding difficulty. His sentences were mostly complete and relevant. His comprehension and repetition were excellent. Three years later, he was reassessed. He was fully oriented, and his memory for recent and remote events was still intact. He still lived in his private home, coped with all activities of daily living, but reported a continuous deterioration of his language. His spontaneous speech contained phonemic paraphasias and was much less fluent. Occasionally he was able to produce short, complete sentences, but his wordfinding difficulty frequently interfered with his ability to complete a sentence. He was not able to generate lengthy descriptive sentences spontaneously. His comprehension was well preserved, but he had some problem reading aloud. He was agraphic and mildly apractic.

Another year later, he was examined a third time. He had moved to a nursing home because of a further decline of his communicative skills. He had difficulty conveying meaningful personal information. He was even unable to give his name and address. His speech fluency had decreased, and his speech contained a great many paraphasic errors as well as automatic phrases, such as "I don't know." Now his language comprehension was also impaired, and he was moderately apractic. He needed help in all activities of daily living, but he was sufficiently oriented in his nursing home. In the following 5 years, his condition deteriorated further. Now 89 years old and severely disabled, he still lives in the nursing home.

PATIENTS 1 AND **2.**— Patients 1 and 2 died 3 years after the onset of language impairment. In both patients, brain autopsy showed moderate global brain atrophy. In patient 1, there was

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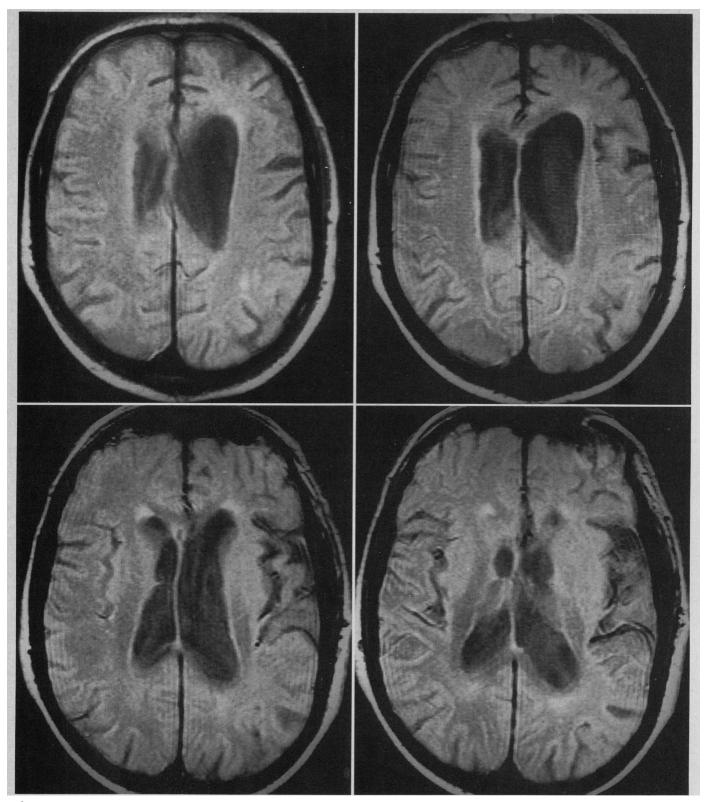


Fig 1.—Four magnetic resonance imaging scans of patient 5, who presented with a 2-year history of speech slowing and word-finding difficulty (see case report in the "Results" section). Scans show atrophy predominantly in the left frontal and left perisylvian cortex.

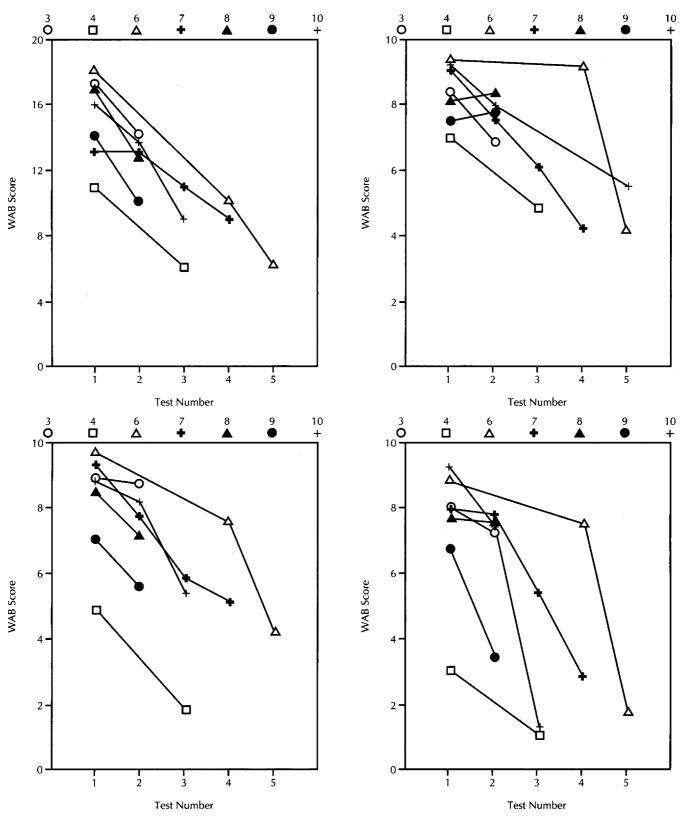


Fig 2.—Longitudinal Western Aphasia Battery (WAB) scores of patients with primary progressive aphasia. The figure shows separately the scores of the four main WAB subcategories: top left, spontaneous speech; top right, comprehension; bottom left, repetition; and bottom right, naming. Test 1 shows the score of the initial test, and tests 2 through 5 show the results on WAB reexaminations 1 to 4 years after the first test. The numbers above the symbols indicate patient number according to Table 1.

Table 3.—DRS Mean Scores of Patients With PPA*						
DRS Score at First Test	Maximum Score Attainable	Mean (±SD) Score of Normal Controls (% of Maximum Score)	Mean (±SD) Score of Patients With PPA (% of Maximum Score)			
DRS score at first test						
Total	144	139±3.4 (97)	99.3±14.6 (69)			
Verbal	97	92.5 ± 3.3 (95)	58.2±15.1 (60)			
Nonverbal	47	46.6±1.0 (99)	41.1±3.5 (87)			
Commands and imitation (items B-D)	10	10.0 ± 0.0 (100)	9.2 ± 1.2 (92)			
Motor performance (items I-O)	7	6.8±0.4 (97)	5.9±1.2 (84)			
Construction (items F-U)	6	5.9 ± 0.3 (98)	5.7±0.5 (95)			
Identities and oddities (item V)	16	15.9±0.3 (99)	13.7±2.3 (86)			
Visual matching and memory (items AJ-AK)	8	8.0±0.0 (100)	7.7±0.5 (96)			
DRS score after 1 yt						
Total	144		76.6±17.7 (53)			
Verbal	97		46.4±15.0 (48)			
Nonverbal	47		32.2±9.2 (69)			

*DRS indicates Dementia Rating Scale; PPA, primary progressive aphasia.

+The DRS results of five patients retested after 1 year are added.

additionally focal marked atrophy in the left superior parietal lobe. In this patient, brain histological examination revealed findings that were commensurate with Pick's disease.²⁶ There was a diffuse neuronal cell loss and gliosis. The subsisting neurons were often enlarged and achromasic. Some neurons contained large cytoplasmic inclusions, which conformed to the classic description of Pick bodies. Furthermore, there were some neurofibrillary tangles and argyrophilic plaques. The histological changes involved the neocortex bilaterally. In comparison with other cortical and subcortical regions, the left parietal and frontal lobes were most severely affected, whereas the hippocampus was almost preserved. In patient 2, the pathological examination of the brain revealed findings that met the criteria for AD of the National Institutes of Health panel.27 There was widespread diffuse neuronal cell loss, gliosis, and quite high density of senile plaques and neurofibrillary tangles. The neurofibrillary degeneration involved all examined neocortical and subcortical areas. In the left middle frontal gyrus, for example, vast numbers of senile plaques, mainly of the diffuse type, were accompanied by overwhelming numbers of neurofibrillary tangles. In some of the deeper cortical laminae, almost every nerve cell showed neurofibrillary degeneration, and the neuritic plaque density exceeded 33 per lowpower microscopic field.

ALL OTHER PATIENTS.—In all other patients, brain lesions were studied using neuroimaging techniques. Brain scans done with the first testing showed mild to moderate cortical atrophy in all cases. In three patients (cases 4, 5, and 9), atrophy involved the left hemisphere more than the right. Figure 1 shows MRI findings in patient 5. Atrophy predominantly affected the left frontal cortex and the left perisylvian region. In agreement with these findings, this patient had an anomic aphasia with reduced fluency score (5/10), while his comprehension score (8.7/10) was more preserved.

RESULTS

The initial WAB confirmed an aphasic language impairment in all patients with PPA. The mean AQ was well below the 93.8 cutoff.²⁸ The WAB classified language impairment in nine of 10 patients with PPA as anomic aphasia. Only one patient had a different aphasia type: patient 4 (Table 1) presented additionally with a distinct decrease in her repetition score and was classified as having conduction aphasia. Table 2 gives the mean WAB data of the PPA group (column 3) and the two reference groups with stroke-caused aphasia (column 4) and with AD (column 5).

As mentioned in the "Subjects and Methods" section, the stroke patient sample was matched for aphasia type so that the WAB scores were in the anomic range in nine of 10 patients and in the conduction aphasia range in one patient. In the AD reference group, eight of 10 patients had an AQ close to the 93.8 cutoff (between 91 and 95), which indicated only a mild language problem. In two patients in the AD reference sample, however, aphasia was a more prominent feature of general cognitive decline. These two patients had AQ scores of 81 and 77, and the language profile was classified in the anomic range.

The statistical comparison revealed that the initial AQ was significantly lower in patients with PPA than in those with AD (P=.007), whereas the difference between PPA and stroke-caused aphasia groups did not reach the level of significance. A comparison of the four subtotals of the language section of the WAB (spontaneous speech, comprehension, repetition, naming) showed that the spontaneous speech score was significantly lower in the PPA group than in both reference groups (P=.0004). Both subcategories of spontaneous speech (information content, fluency) contributed to this finding, though to a somewhat different extent. The fluency mean score was significantly lower in patients with PPA in comparison with both reference groups (P=.0024). Statistical comparison of the information content mean score found the difference between PPA and AD groups to be significant (P=.006), but the difference between PPA and stroke-caused aphasia groups was not. Comparing the other three subtotals (comprehension, repetition, naming) revealed no significant differences. When the subtests of comprehension and naming were studied, only object naming showed a remarkable difference. The statistical analysis showed borderline significance (P=.01) for the difference between the PPA group and both reference groups. On object naming, patients with PPA tended to have difficulty performing any verbal response rather than using circumlocutions or paraphasias.

Table 2 also presents the data of the other WAB subtests. Some of these subtests showed mild impairment in the PPA group. Statistical comparison among the three groups found no significant difference in any of the subtests, ie, PPA, stroke-caused aphasia, and AD group patients did not perform significantly differently in reading, writing, praxis, drawing, block design, and RCPM. The RCPM mean score of 19.9 ± 7.1 in patients with PPA was in the normal range, corresponding to a 54th percentile after ad-

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justment for age. Eight patients ranged between the 28th and 91st percentiles. Two patients were below the 20th percentile according to their age (cases 2 and 8).

The DRS data in Table 3 give further information about the profile of cognitive decline in PPA. The first column gives the maximum score that could be reached; the second column, the mean scores of 10 healthy elderly volunteers (three women, seven men; mean age, 73.3 ± 6.3 years) who were tested in our department. The total DRS score of patients with PPA was clearly below normal. However, the DRS comprises many items that require language output so that reduced language skills, especially an expressive language disability, may have influenced the total score. The rest of the table therefore separates those items that do require verbal answers from those that do not. The data show that patients with PPA were less impaired in the nonverbal part of the test, ie, they performed correctly on 60% of the verbal but on 87% of the nonverbal items. On the nonverbal tests, all patients with PPA performed within normal limits on construction (95%) and on visual matching and memory (96%).

Seven of 10 patients with PPA were retested one or more times following the first assessment. Table 1 gives the AQ of the initial and last administered WABs. Figure 2 shows the longitudinal scores of the four WAB subtotals (spontaneous speech, comprehension, repetition, naming). It is quite obvious that all patients with PPA who were retested continuously deteriorated on all language subtotals. Spontaneous speech and naming scores seemed to decrease somewhat faster than comprehension score. However, all patients who were retested more than 1 year after the first assessment eventually reached the level of global aphasia. There was no clear-cut fluent vs nonfluent distinction in these advanced stages of PPA. Table 3 gives the DRS findings of the five patients who were retested 1 year after the first assessment. Total DRS mean score had dropped to 76.6 ± 17.7 (53% of 144), but the verbal items (48%) were again more deteriorated than the nonverbal items (69%). In eight of 10 patients, global dementia developed between 3 and 7 years after the onset of PPA. "Global dementia" was defined according to the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition criteria for "mild dementia," with criterion B(3) (other disturbances of higher cortical function, such as aphasia, etc) being excluded.²⁹ In addition to Table 1, case reports on two patients give further information: patient 5, whose MRI scans are shown (Fig 1), and patient 6, whose longitudinal study involved initial findings in an early stage of PPA.

COMMENT

The present study investigates profiles of language impairment in 10 patients with PPA using standardized neuropsychological test batteries (WAB, DRS). The study confirms the suggestion that anomia, mild agrammatism, and impaired fluency are the most common characteristics of PPA.^{2,3} Anomic aphasia was the predominant syndrome when patients were first seen. In early stages, patients with PPA were typically complaining of difficulty in expressing themselves and in finding the right word. On the initial WAB, spontaneous speech and especially fluency scores were significantly more affected in patients with PPA than in patients with anomic aphasia after left middle cerebral artery stroke or in patients with AD. Spontaneous speech in patients with PPA was typically slow, hesitant, and sometimes agrammatic. Furthermore, a low score in object naming reflected a word-finding deficit. In contrast to reduced verbal output, language understanding was more preserved.

This pattern of language impairment is commensurate with the predominant findings in previous PPA studies. In his initial study, Mesulam¹ described anomic aphasia in five of six patients. Logopenia and long word-finding pauses occurred in four of six patients, while auditory comprehension was relatively preserved. Weintraub et al³ investigated aphasia profiles in four patients with PPA. In agreement with the present findings, reduced speech fluency and phonemic paraphasic errors were typical features in PPA. Green and coworkers9 did a major study that included eight patients with PPA. Expressive language problems characterized by dysnomia and slow, hesitant speech were found in all patients. However, the studies of Mesulam and Green et al also included one patient whose major problem was a language comprehension deficit. Poeck and Luzzatti¹⁰ extensively analyzed three patients with PPA and reviewed the literature. All three patients were classified as having "amnesic aphasia" on the initial language test, but they were relatively fluent, and one of them also had a marked comprehension deficit. Referring to their own three patients and to another 29 cases (including the six patients of Mesulam cited above), Poeck and Luzzatti denied the existence of a unitary syndrome in PPA. However, they admitted that the majority of cases exhibited amnesic aphasia before a semantic breakdown led to a more severe syndrome.

Snowden et al³⁰ recently published a study of progressive language disorder due to lobar atrophy. In contrast to the present study, Snowden et al also included patients who had changes of personality, such as increased aggressivity or a loss of insight and affect, and even a case of progressive parkinsonism. In agreement with the present findings, Snowden et al found anomia to be a prominent feature of progressive aphasia in all patients. There was also an impairment of spontaneous speech in the course of the disease so that the language disorder eventually progressed to mutism. In contrast to our series of patients with PPA, Snowden et al found quite a variety of symptoms, but some of the patients were seen in later stages. In some cases, language comprehension was predominantly impaired. However, Snowden et al do not provide any formal language test data so a comparison with the aphasia profiles of our study is limited.

In the initial concept,¹ PPA preferentially started in presenium. The cognitive decline in PPA was assumed to be slower and more benign than in other degenerative disorders such as AD. Several recently published investigations, however, have found that PPA can also have a senile onset and a more rapid deterioration.^{7,9,10} The majority of our patients with PPA were in senium, and the progression of the disease was quite rapid in the majority of cases. In our series, all patients had considerably deteriorated each time they were retested so that some of them eventually reached the level of global, severe aphasia. Concerning the prognosis of PPA, our data therefore support the observation that PPA often is a precursor of global deterioration.⁹

Another important feature of PPA is the absence of global dementia. The diagnosis of PPA requires preserved nonverbal cognitive skills along with the aphasic language disorder. Previous investigators have emphasized the importance of a formal assessment of aphasia-independent

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intellectual skills,^{10,31} but it has been a major problem to create test batteries of cognitive skills that are not influenced by aphasia. Studies of aphasic and apractic subjects have shown evidence that tests such as RCPM, which do not require verbal answers, are adversely affected by both aphasia and apraxia.³² In the present series, patients were only admitted when there was no clinical evidence of global dementia. No patient was confused, and all still coped with activities of daily living when they were first tested. Patients were included or excluded on the basis of the history and the clinical findings. The investigation of typical test profiles was the major goal of the present PPA study. Therefore, neuropsychological test scores were not used as a priori exclusion criteria. The DRS was administered to evaluate the degree of global mental deterioration. Information about cognitive skills other than language was dissociated by separately analyzing test items of the WAB and DRS that do not depend on verbal answers. It is remarkable that patients with PPA reached even slightly higher mean scores in drawing, block design, and calculation than the reference sample of stroke aphasics, though the differences were not significant (Table 2). Also on the RCPM, there was no significant difference between patients with PPA and both reference groups. Patients with PPA performed on average in the normal range, but some had low-normal performances and two even scored below the 20th percentile.

These findings in patients with PPA agree with previous observations that investigated the influence of aphasia on the performance on RCPM. Anomic and conduction aphasics showed on average mildly deteriorated scores on RCPM, similar to patients with diffuse brain damage or right hemisphere lesions.³³ On the DRS, patients with PPA were clearly in the pathological range when the total score was considered. However, there was a distinct difference between the verbal and nonverbal part of the DRS. On initial testing, patients with PPA correctly accomplished 87% of the nonverbal items, but only 60% of the verbal ones. All patients with PPA performed normally on the construction and visual matching and memory items. Thus, the DRS findings supported the clinical impression that PPA spared nonverbal cognitive skills (Table 3).

Besides the dissociation of verbal and nonverbal impairment, the present study stresses the different profile of language impairment in PPA in comparison with typical findings in AD. In AD, aphasia is a common feature, and its prevalence increases with severity of dementia, reaching virtually 100% when the final stages are included.^{34,35} Previous studies of aphasia in AD already suggested differences in language profile between AD and PPA. Measures of comprehension and written expression were decreased in AD-associated aphasia, whereas other components, including confrontation naming, were less affected.³⁵ Cummings et al³⁶ summarized the typical language impairment in AD as transcortical sensory aphasia. Quite opposite to the present findings in PPA, patients with AD had fluent paraphasic output and impaired auditory comprehension. Spontaneous speech in patients with AD had a rather normal phrase length, grammatical competence, and melodic line.³⁶ In comparison with patients with stroke-caused aphasia, patients with AD had a distinctly poorer comprehension with more fluent speech output and a high incidence of circumlocutions and semantic jargon.34

gest that PPA typically starts affecting anterior parts of the language-dominant cortex. The general progression of aphasia indicates that the underlying degenerative disorder became more extensive in the majority of cases. In the present study, MRI and computed tomography were used to investigate lesions in early stages of PPA. In patient 5, for example, a nonfluent anomic aphasia had developed for about 2 years. Receptive language was still preserved. In agreement with these findings, MRI showed cortical atrophy especially involving left frontal and perisylvian cortex. These findings are commensurate with previous studies of cerebral blood flow using single photon emission computed tomography. In these studies, a hypoperfusion was found that predominantly affected frontal and perisylvian regions of the left cerebral hemisphere.^{8,14} In follow-up studies, the initial focus of hypoperfusion progressively extended to involve eventually most of the ipsilateral hemisphere and the contralateral frontal lobe.⁸ Studies of cerebral glucose metabolism using positron emission tomography in five cases^{11,16} also demonstrated special alteration of the left hemisphere in PPA, but they did not show a special metabolic deterioration in the frontal cortex.

The results of the follow-up testing already suggested that neuronal degeneration in most of our cases did not remain restricted to one brain area. In the present sample, brain autopsy was performed in two cases. In patient 1, the neuropathological examination revealed Pick's disease, which predominantly involved the left parietal and frontal cortex. In comparison with previous studies of PPA and Pick's disease,^{17,20} the preservation of the hippocampus was quite remarkable in our patient. In patient 2, neuropathological findings were commensurate with the diagnosis of AD. This was not the first case where AD obviously started with PPA. Other investigators also found AD changes in patients with PPA.9,18,21 Thus, the present study contributes to the following observations: PPA can be a precursor of global dementia, but degenerative diseases other than AD occur quite frequently. Although PPA is associated with a heterogeneous underlying disease, the initial profile of language impairment in PPA suggests a specific lesion site.

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