Frontotemporal Decreases in rCBF Correlate with Degree of Dysnomia in Primary Progressive Aphasia

Elmer C. San Pedro, Georg Deutsch, Hong Gang Liu, and James M. Mountz

Department of Radiology, Division of Nuclear Medicine, University of Alabama at Birmingham Medical Center, Birmingham, Alabama

Primary progressive aphasia (PPA) is an uncommon degenerative dementia characterized by gradual impairment of language function with initial sparing of the memory domain. Using semiquantitative ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO) brain SPECT as a measure of regional cerebral blood flow (rCBF), we investigated the relationship between reduced ^{99m}Tc-HMPAO uptake and the severity of dysnomia in PPA. **Methods:** Seven right-handed patients with PPA had their dysnomia assessed by the Boston Naming Test (BNT), a subtest of the Boston Diagnostic Aphasia Examination. Neuroimaging studies, including ^{99m}Tc-HMPAO brain SPECT, CT, and MRI, were performed. Correlational analysis between reduced rCBF and BNT was performed. **Results:** Brain SPECT showed a reduction in ^{99m}Tc-HMPAO uptake involving the frontal and temporal lobes in all 7 patients. CT and MRI showed mild to moderate cerebral atrophy in 4 patients. Low scores on the BNT correlated with low frontotemporal ^{99m}Tc-HMPAO (Spearman $r = 0.97$, $P = 0.004$) in the 5 patients with left-hemisphere involvement. **Conclusion:** Decreased rCBF to the frontotemporal region characterized the cerebral abnormalities associated with PPA. The finding of focal rCBF abnormalities in the right hemisphere of 2 right-handed women corroborates that PPA symptoms may arise from a "non–left-dominant"-hemisphere degenerative process. Our results support the usefulness of rCBF SPECT imaging as a diagnostic aid in PPA.

Key Words: progressive aphasia; ^{99m}Tc-HMPAO brain SPECT; Boston Naming Test

J Nucl Med 2000; 41:228–233

Primary progressive aphasia (PPA) is an uncommon type of degenerative dementia characterized by gradual impairment of language function that remains neuropsychologically focal for several years with sparing of the memory domain (*1*). Compared with other neurodegenerative disorders, which initially affect cognition followed by language impairment, many patients with PPA retain their cognitive functions, allowing them to continue with their activities of daily living (*1*). "Word-finding" or "naming" difficulty (dysnomia) is the most common and early clinical presentation of PPA (*2*). Other language impairment, such as reading and writing, decreased comprehension of spoken word, and poverty of words, may also be present (*2*). Dementing illnesses, such as Pick's disease and Alzheimer's disease (AD), may present with language impairment; however, patients with AD usually show decreases in comprehension and written expression to a greater extent than they show "word-finding" difficulty (*3*). Additionally, spontaneous speech is significantly more impaired in patients with PPA in comparison with patients with AD. Aphasia in PPA tends to affect anterior parts of the language-dominant cortex (*4*). However, at the late stages there is an overlap of symptoms, and the clinical distinctions between AD, Pick's disease, and PPA are clinically less clear.

Neuroimaging studies using MR and CT have shown selective atrophy in the left perisylvian region in most patients with PPA (*5*). Previous studies using FDG PET and ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO) SPECT showed frontal and temporal lobe abnormalities before changes were apparent on MRI (*6–8*). However, none of these studies performed correlational analysis between clinical dysnomia and the degree of functional deficit on FDG PET or ^{99m}Tc-HMPAO SPECT. The objective of this study was to determine whether there is a relationship between the degree of word-finding difficulty in PPA and the degree of decreased frontotemporal ^{99m}Tc-HMPAO uptake using semiquantitative brain SPECT.

MATERIALS AND METHODS

Study Population

Seven right-handed patients (4 men, 3 women; age range 59–77 y; mean age, 65.6 y) diagnosed with PPA were referred to the Division of Nuclear Medicine for ^{99m}Tc-HMPAO brain SPECT to assess disease severity. The duration of illness at the time of SPECT imaging was 2–7 y (mean, 2.9 y). The patients presented with varying degrees of dysnomia (Table 1). All patients satisfied the criteria for PPA, i.e., language impairment without accompanying cognitive disorder in at least the first 2 y of disease (*1*).

Boston Naming Test

All subjects were evaluated for dysnomia using the Boston Naming Test (BNT), which is a part of the Boston Diagnostic Aphasia Examination (*9*). It is a visual confrontation naming task

Received Oct. 13, 1998; revision accepted Jul. 21, 1999.

For correspondence or reprints contact: James M. Mountz, MD, PhD, University of Alabama at Birmingham Medical Center, Division of Nuclear Medicine, 619 S. 19th St., JT J260, Birmingham, AL 35233-6835.

TABLE 1
Clinical Data on 7 Patients with PPA

Patient no.	Age (y)	Sex	Duration of PPA* (y)	Presentation	BNT score	MRI or CT
1	59	M	3	Dysnomia	54	CT, atrophy
2	71	M	2	Dysnomia, ↓ speech fluency	35	CT, normal
3	60	F	2	Dysnomia	30	CT, normal
4	77	M	2	Dysnomia, ↓ speech fluency	18	MRI, atrophy
5	65	M	2	Dysnomia, ↓ speech fluency	14	CT, atrophy
6	64	F	7	Tripping over words, ↓ speech fluency	50	MRI, atrophy
7	63	F	2	Dysnomia, ↓ speech fluency	45	MRI, normal
Mean	65.57		2.9			

*Duration of PPA indicates time interval between occurrence of first symptoms to diagnosis. Patients presented with varying degrees of dysnomia.

and is scored according to a standard procedure, wherein subjects are asked to name line drawings of common objects (*9*). The maximum score on the BNT is 60. In this study, dysnomia is considered mild if the BNT score is 40–60, moderate if 30–40, and severe if <30.

Neuropsychological Testing

Neuropsychological assessment included Aphasia Series, Apraxia Series, Beck Depression Inventory, Dementia Rating Scale (Mattis), Weschler Adult Intelligence Scale–Revised (WAIS-R), and Weschler Memory Scale–Revised.

CT and MRI

Non–contrast-enhanced CT was performed on 4 patients (Table 1) using a GE CTI scanner (General Electric, Milwaukee, WI). MRI was performed on the remaining 3 patients (Table 1) using a GE Signa Advantage (General Electric) 1.5-T scanner.

^{99m}Tc-HMPAO Brain SPECT

All 7 subjects underwent ^{99m}Tc-HMPAO brain SPECT to assess regional cerebral blood flow (rCBF). Approximately 740 MBq (20 mCi) ^{99m}Tc-HMPAO were injected intravenously, with patients in the resting state with eyes closed in a dim, quiet room. Imaging was performed on the Picker Prism 3000XP (Picker International, Bedford, OH) triple-head γ camera, equipped with low-energy, high-resolution collimators yielding an image resolution of approximately 7 mm full width at half maximum. The matrix size was 128 × 128 (pixel size, 2.0 mm on edge). Acquisition parameters were 120° rotation, 40 stops/head at 45 s/stop (120 total projections). Image attenuation correction was performed using the Chang method, and reconstruction was performed using a Butterworth filter with frequency cutoff of 0.225 and Nyquist order of 6 (*10*). Transverse sections were reconstructed parallel to and sequentially above the canthomeatal line (CM) as defined by the Mountz reference system (Harrison Medical, Helena, AL) routinely used in the Division of Nuclear Medicine (*11*).

rCBF SPECT Semiquantitative Analysis

Region of Interest Definition. Because the pathologic abnormality in PPA predominantly affects the perisylvian regions to a greater extent than other areas of the brain, semiquantification was performed on CM line + 5.5 cm (*2*). This level encompasses important cortical (Brodman) areas of the brain responsible for language function that are known to be involved in early PPA (Fig. 1A). Region of interest (ROI) count data from the perisylvian territory (frontotemporal region) represented by regions 2–4 (left hemisphere) and 9–11 (right hemisphere) were obtained and are shown in Table 2.

Cortical Circumferential Profile. Cortical circumferential profiles were obtained by delineating an annular ring of cortex 1.6 cm (8 pixels) wide using a computer-automated algorithm. The outer boundary of this annulus was defined by a pixel threshold of 50% of the average pixel value for the entire section under analysis. Individual cortical ROIs were created by subdividing this annulus into 12 equal angular sectors (Fig. 1C). The rCBF value for each ROI was calculated by a normalization procedure, in an which the total pixel counts in each ROI were divided by the average of the top 90% of the cerebellar pixel counts (Fig. 1B) and compared to 9 age- and sex-matched healthy controls analyzed in an identical manner (*12,13*). We have shown that the major lobar regions of the brain can be assessed using this method of ROI characterization (*14*).

On section CM + 5.5 cm, regions 1–3 represent the left frontal lobe and regions 10–12 represent the right frontal lobe. Region 4 represents the left superior temporal lobe and region 9, the right superior temporal lobe. Regions 5–6 and 7–8 represent the occipital lobes in the left and right hemispheres, respectively (Fig. 1C) (*14*). Regions 5–6 and 7–8, which represent the left and right occipital regions, were not included in the analysis, because this area is rarely involved in PPA (*2*). Regions 1 and 12 were also excluded because they do not correspond to known Brodman language areas (Fig. 1A).

Because the typical presentation of PPA involves the language-dominant left hemisphere, statistical analysis was performed only on a subgroup of 5 patients with left frontotemporal diminution of ^{99m}Tc-HMPAO uptake (Table 2).

RESULTS

Boston Naming Test and Neuropsychological Testing

Table 1 shows the results of the 60-item confrontation naming test; a score of <45 is indicative of significant dysnomia (*15*). Our patient population had mild (n = 3), moderate (n = 2), and severe (n = 2) degrees of dysnomia (*16*). Five of the 7 patients had nonfluent aphasias. None of the patients showed depression on the Beck Depression Inventory. None of the patients showed memory or cognitive decline on Mattis, WAIS-R (selected subtests), or Weschler Memory Scale–Revised.

CT and MRI

Three patients (Table 1) had normal CT or MRI scans for age. Two of the 4 patients (Table 1) who underwent CT had

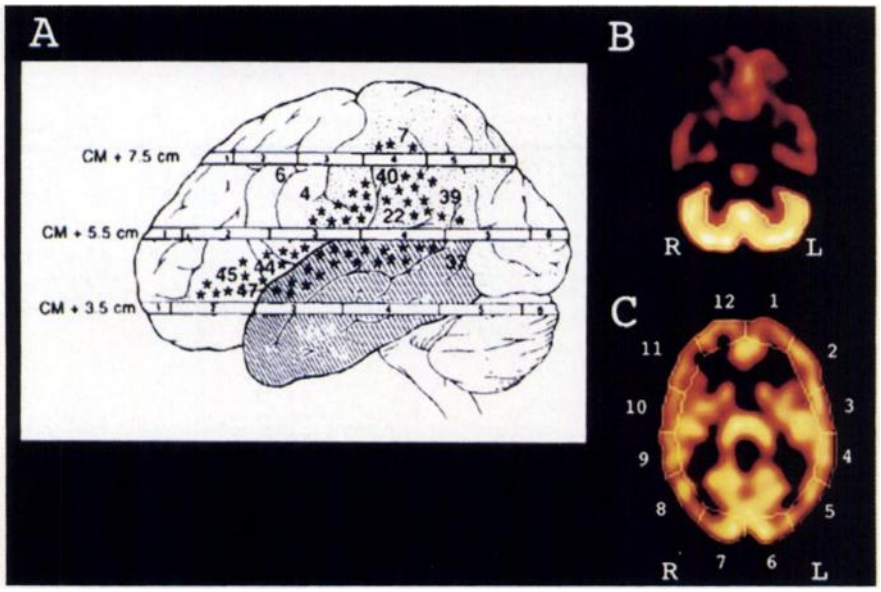

FIGURE 1. (A) Left lateral brain diagram with Brodman areas considered to have language function, showing extent of cortical involvement (asterisks) in progressive aphasia. Area surrounding perisylvian region extending from frontal to temporal lobes has been reported to be involved in PPA. Diagram also illustrates level of section, 5.5 cm above CM (CM + 5.5 cm), where semiquantification was performed. Section is positioned at center of brain and allows measurement of count data in frontal lobe, perisylvian region, and temporal lobe. (B) Example of cerebellar ROI used for count normalization. (C) Twelve cortical ROIs, clockwise (1–12), used to divide transverse SPECT slice. ROIs 1–2 represent left frontal lobe; region 3 represents frontotemporal cortex; region 4 represents left temporal lobe. Regions 5 and 6 represent occipital lobe, which is rarely reported to be involved in PPA.

mild to moderate atrophy. Two of the 3 patients who underwent MRI were also found to have mild atrophy commensurate for age (Table 1). A CT scan of a 59-y-old man (Table 1) with progressive aphasia is shown in Figure 2. The CT scan showed mild age-related cerebral atrophy.

Semiquantitative rCBF SPECT

Patients 1–5 (Table 2) represent a subgroup who showed left-hemispheric hypoperfusion on SPECT. Cortical-to-cerebellar count ratios for regions 2–4 (left perisylvian) and 9–11 (right perisylvian) are shown. Reduction in ^{99m}Tc-HMPAO uptake in the left perisylvian, frontal, and temporal lobe regions was seen in this subgroup. Figure 2 is a representative ^{99m}Tc-HMPAO SPECT scan.

Figure 3 (Table 2) shows an atypical right-hemispheric hypoperfusion of the frontal and temporal region in PPA. The patient is a 64-y-old schoolteacher who had PPA for 7 y with gradual decrease in fluency but with intact cognitive function (Mini-Mental State Examination [MMSE] score, 28/30). The brain SPECT shows hypoperfusion to the right frontal, perisylvian, and temporal lobe regions.

In the 3 patients (Table 1) who had normal CT or MRI

TABLE 2
Cortical-to-Cerebellar ROI Count Ratios in 7 Patients with Progressive Aphasia Obtained at CM + 5.5 cm

Patient no.	Left hemisphere ROI				Right hemisphere ROI			
	2	3	4	Mean	9	10	11	Mean
1	0.78	0.77	0.82	0.79	0.81	0.83	0.80	0.81
2	0.74	0.71	0.80	0.75	0.84	0.86	0.96	0.89
3	0.72	0.84	0.70	0.75	0.82	0.83	0.81	0.82
4	0.74	0.67	0.74	0.72	0.85	0.87	0.86	0.86
5	0.73	0.66	0.71	0.70	0.86	0.83	0.81	0.83
6	0.84	0.82	0.86	0.84	0.67	0.74	0.72	0.71
7	0.82	0.79	0.69	0.77	0.68	0.73	0.76	0.72
Patient mean ± 1 SD	0.76 ± 0.02	0.75 ± 0.07	0.75 ± 0.06		0.84 ± 0.02	0.84 ± 0.02	0.85 ± 0.07	
Control mean ± 1 SD	0.88 ± 0.07	0.88 ± 0.06	0.85 ± 0.03		0.87 ± 0.08	0.90 ± 0.09	0.88 ± 0.09	

Patient mean was calculated only for patients 1–5, who showed unilateral left frontotemporal diminution on ^{99m}Tc-HMPAO SPECT. Patients 6 and 7 were excluded because they showed right hemispheric and bilateral involvement, respectively. Mean count ratios for first 5 patients are lower than age-matched normal controls analyzed in an identical manner (*13*).

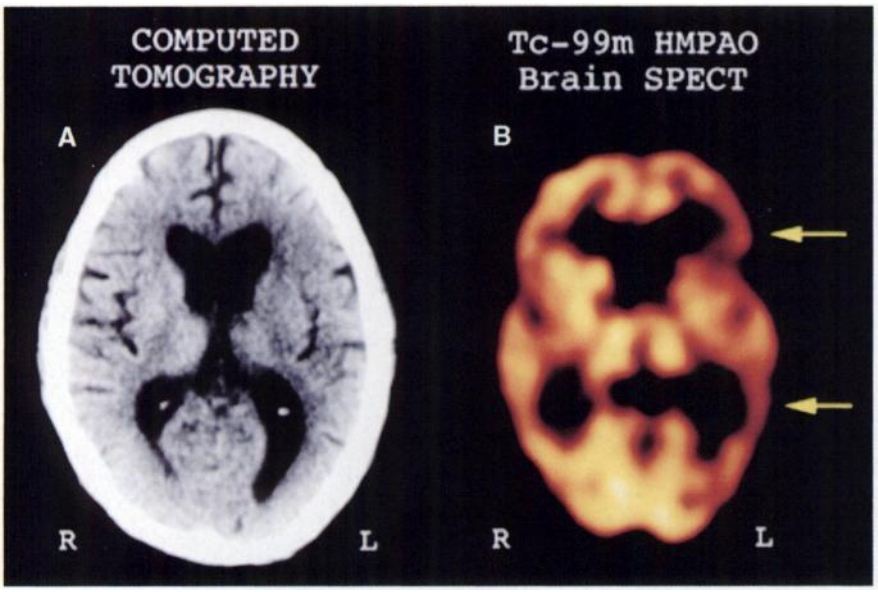

FIGURE 2. CT (A) and ^{99m}Tc-HMPAO brain SPECT scans (B) of 59-y-old man with mild dysnomia (patient 1; Table 1). Patient presented with word-finding difficulty of 2-y duration. He has no comprehension problem with written or spoken words; however, he reports that "words cannot come out" when he tries to speak. His neurological and cognitive examinations are normal, and he is able to perform activities of daily living without assistance. He scored 54 on BNT. Reduction in rCBF to left perisylvian, frontal, and temporal lobes (arrows) characteristic of progressive aphasia is identified on ^{99m}Tc-HMPAO SPECT. CT scan shows mild atrophy.

scans for age, there was decreased ^{99m}Tc-HMPAO uptake on brain SPECT (Table 2).

Figure 4 (Table 1) exemplifies the reduction in ^{99m}Tc-HMPAO uptake accompanied by a normal MRI. The patient is a 63-y-old woman with mild dysnomia (BNT = 45). She presented with increasing difficulty in saying certain words. She had a tendency to hesitate when speaking and had difficulty writing, particularly when spelling multisyllable words.

Brain rCBF SPECT and BNT

Correlations between rCBF ratios and BNT scores were performed for the 5 patients with unilateral left-hemispheric involvement. Spearman rank correlation test demonstrated a parallel relation between mean left rCBF count ratio (Table 2) and the severity of dysnomia (Table 1) ($r = 0.97$; $P = 0.004$).

DISCUSSION

Word-finding difficulty or dysnomia is the failure to retrieve a specific word to express oneself in an ongoing conversation. It is the earliest and most common presentation of progressive aphasia. As the disease progresses, characteristic language impairment, such as impaired fluency, disintegration of syntax, and phonemic paraphasias, emerge (*4,17*). Left-hemispheric involvement in PPA is well documented by neuroimaging and histopathological studies in accord with the fact that language function is primarily localized in the left hemisphere among right-handed individuals.

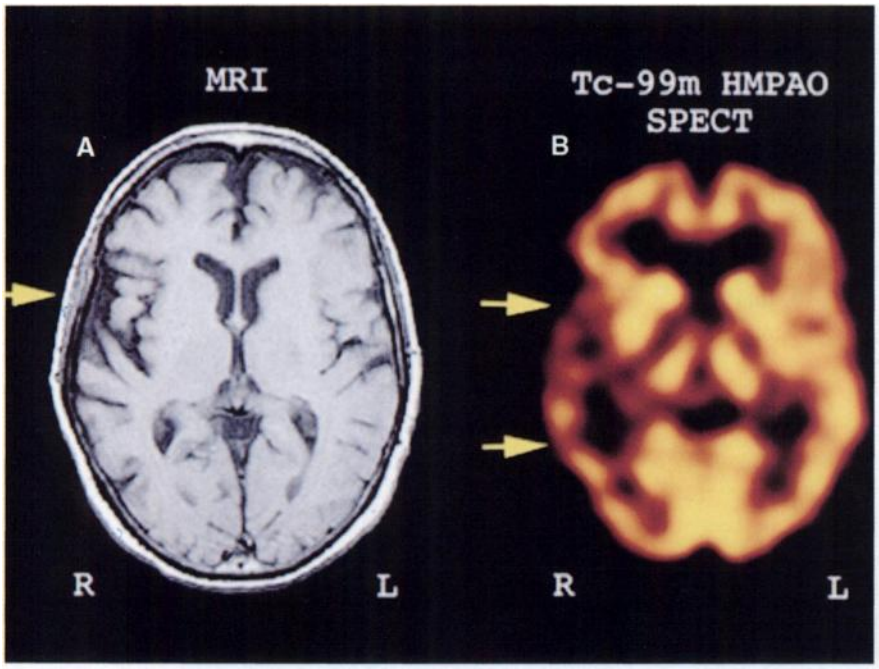

FIGURE 3. MR image (A) and ^{99m}Tc-HMPAO brain SPECT scan (B) of 65-y-old woman with mild degree of dysnomia (patient 6; Table 1). She presented with 7-y history of "tripping" over words. Initially, she had trouble with multisyllable words but currently has difficulty even with single-syllable words. She reports problems with decreasing fluency. She claims to know what she wants to say but is "not able to get the words out." She onced played the piano and sang with accompaniment but lately reports loss of interest because of her inability to get right tune. She scored 30 of 30 on MMSE. Right frontotemporal region shows atrophy on MR image and reduced rCBF on SPECT. There is larger area of right frontotemporal hypoperfusion on rCBF SPECT (lower arrow) than atrophy shown on MR image.

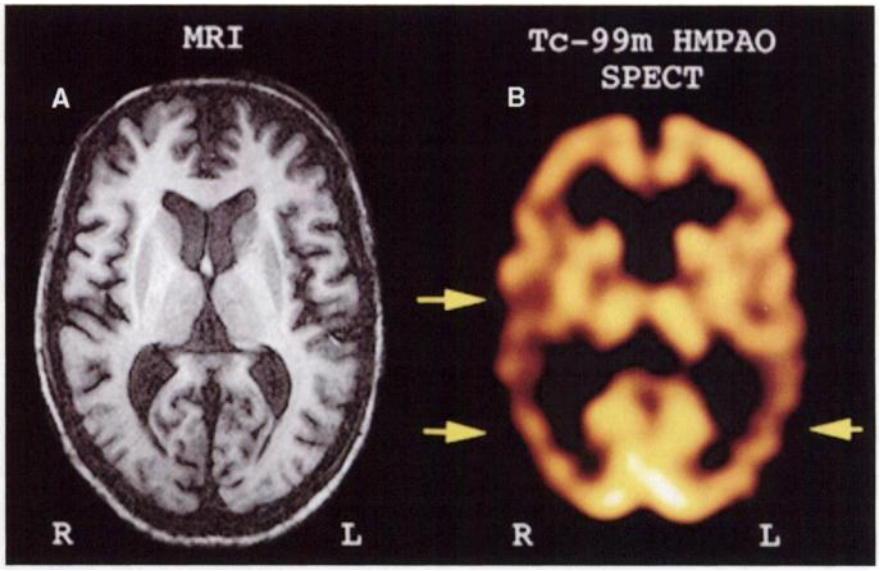

FIGURE 4. MR image (A) and ^{99m}Tc-HMPAO SPECT scan (B) of 63-y-old woman with mild dysnomia (BNT = 45). Patient presented with history of slowly progressive difficulty with expressive language, with difficulty finding nouns and producing words for past 2 y. She reports increasing difficulty saying certain words. She has tendency to hesitate when speaking and has difficulty writing, particularly when spelling multisyllable words. Battery of neuropsychological examinations failed to show any cognitive impairment except for language deficits. SPECT shows bilateral temporal lobe and right posterior frontal reduction (arrows) in ^{99m}Tc-HMPAO uptake. MR image is normal.

Language Impairment and ^{99m}Tc-HMPAO SPECT

In this series of 7 right-handed patients, 5 showed left-hemispheric reduction in ^{99m}Tc-HMPAO uptake, 1 showed unilateral right-hemispheric reduction, and 1 showed bilateral temporal lobe and right frontotemporal reduction.

Among the patients with left-hemispheric involvement, the strong association between scores on the confrontation naming test and the reduction of ^{99m}Tc-HMPAO uptake on SPECT indicates that the focal rCBF abnormalities observed indeed reflect the degenerative process underlying the progressing aphasia. ^{99m}Tc-HMPAO SPECT may be useful in diagnosing ambiguous cases and in following the progression of the disease. Involvement of the frontal lobe region has been shown to accompany PPA. In this study, reduction in ^{99m}Tc-HMPAO uptake in this region correlates with low BNT scores.

Language impairment arising from right-hemispheric degeneration in a right hander is very unusual. Patient 6 may represent a case of right-hemisphere language dominance in a right hander, a relatively rare situation with less than 5% incidence (*18*). Aphasia arising from bilateral brain injury is clearly not unexpected; the presence of focal bilateral degeneration resulting in primarily aphasic symptoms in patient 7 is atypical of most previously reported cases of PPA. The finding of focal rCBF abnormalities in the right hemisphere of 2 right-handed patients suggests that PPA symptoms may arise from other than a left-hemisphere (language-dominant) degenerative process.

It should be noted that both the right (patient 6) and bilateral (patient 7) PPA cases reported here are women, raising the possibility that the language deficit in these cases is, at least, in part, explained by the greater bilateral representation of language in women (*15*). More recent studies using the Wada amobarbital technique suggest that many previously reported cases of right-hemisphere speech actually represent cases of bilateral speech organization (*19*). Patient 6 may have extensive language representation and this may also explain her relatively mild language deficit, despite the fact that she had the disease for 7 y. The more severe language impairment of patient 7 arising from less severe but bilateral hemispheric rCBF deficits is consistent with bilateral language representation among women.

A recent study using stereological volume measurements has shown that women have proportionally larger language-associated regions (Wernicke's and Broca's areas) compared with men (*20*). This may offer an alternative explanation as to why men are more affected by PPA than women.

The ^{99m}Tc-HMPAO SPECT study showed cortical abnormalities of various degrees around the perisylvian region in all patients. Structural imaging with CT or MRI, however, identified only 4 patients with some degree of atrophy. ^{99m}Tc-HMPAO SPECT is more sensitive than MRI or CT in characterizing the cortical abnormalities in PPA. The cortical abnormalities observed on SPECT in cases in which CT or MR images are normal or just mildly atrophic probably represent early neurometabolic defects involving the frontal and temporal (perisylvian) regions in this disease.

rCBF is related to neuronal activity, whereas brain atrophy is the result of neuronal loss. In Figure 4 there is reduction of rCBF in areas in which there is no cerebral atrophy. In Figure 2 there is very mild atrophy on CT. However, there is significant reduction of rCBF to the left side of the brain. Finally, in Figure 3, there is greater hypoperfusion to the right posterior temporal lobe than the atrophy shown on MRI. These cases suggest that there may be a gradual progression of cerebral changes in PPA from a decrease in neuronal activity (as indicated by a decrease in rCBF), without accompanying cerebral atrophy, to a more advanced stage involving cerebral atrophy. Because ^{99m}Tc-HMPAO SPECT is a sensitive indicator of both decreased neuronal activity and atrophy, it has the capability for early disease detection.

CONCLUSION

^{99m}Tc-HMPAO SPECT may be useful in evaluating patients with progressive language impairment in whom early PPA or another dementia is being considered. Since language impairment can be a predominant sign in various forms of dementia, rCBF SPECT is useful in characterizing the blood flow abnormalities that can distinguish different types of dementias. Clinical dysnomia may have a neuropathologic correlate in the frontotemporal lobe region, the severity of which may be evaluated with semiquantitative rCBF SPECT. In addition, our data show that PPA may demonstrate rCBF abnormalities not only in the language-dominant left hemisphere but may also involve the right hemisphere and can be bilateral.

ACKNOWLEDGMENTS

This work was supported in part by National Institutes of Health grants RO1-AG 06432 and RO1-HD 32100. The authors thank Eva M. Gilliam for expert secretarial assistance and Anthony Zagar for the illustrations.

REFERENCES

1. Mesulam MM, Johnson N, Grujic Z, Weintraub S. Apolipoprotein genotypes in primary progressive aphasia. *Neurology.* 1997;49:51–55.
2. Westbury C, Bub D. Primary progressive aphasia: a review of 112 cases. *Brain Lang.* 1997;60:381–406.
3. Pogacar S, Williams RS. Alzheimer's disease presenting as slowly progressive aphasia. *Rhode Island Med J.* 1984;67:181–185.
4. Karbe H, Kertesz A, Polk M. Profiles of language impairment in primary progressive aphasia. *Arch Neurol.* 1993;50:193–201.
5. Chawluk JB, Alavi A. Neuroimaging of normal brain aging and dementia. In: Greenberg JO, ed. *Neuroimaging: A Companion to Adams and Victor's Principles of Neurology.* New York, NY: McGraw-Hill; 1995:235–382.
6. Chawluk JB, Mesulam MM, Hurtig H, et al. Slowly progressive aphasia without generalized dementia: studies with positron emission tomography. *Ann Neurol.* 1986;19:68–74.
7. Delecluse F, Andersen AR, Waldemar G, et al. Cerebral blood flow in progressive aphasia without dementia. *Brain.* 1990;113:1395–1404.
8. McDaniel KD, Wagner MT, Greenspan BS. The role of brain single photon emission computed tomography in the diagnosis of primary progressive aphasia. *Arch Neurol.* 1991;48:1257–1260.
9. Goodglass H, Kaplan E. *The Assessment of Aphasia.* Philadelphia, PA: Lea & Febiger; 1983.
10. Liu HG, Harris JM, Inampudi C, Mountz JM. Optimal reconstruction filter parameters for multi-headed brain SPECT: dependence on count activity. *J Nucl Med Technol.* 1995;23:251–254.
11. Mountz JM, Wilson MW, Wolff CG, Deutsch G, Harris JM. Validation of a reference method for correlation of anatomic and functional brain images. *Comput Med Imaging Graph.* 1994;18:163–174.
12. Liu HG, Mountz JM, Inampudi C, San Pedro EC, Deutsch G. A semiquantitative cortical circumferential normalization method for clinical evaluation of rCBF brain SPECT. *Clin Nucl Med.* 1997;22:596–604.
13. Deutsch G, Mountz JM, Katholi CR, Liu HG, Harrell LE. Regional stability of cerebral blood flow measured by repeated technetium-99m-HMPAO SPECT: implications for the study of state-dependent change. *J Nucl Med.* 1997;38:6–13.
14. Mountz JM, Tolbert LC, Lill DW, Katholi CR, Liu HG. Functional deficits in autistic disorder: characterization by technetium-99m HMPAO and SPECT. *J Nucl Med.* 1995;36:1156–1162.
15. Springer SP, Deutsch G. *Left Brain, Right Brain: Perspectives from Cognitive Neuroscience.* 5th ed. New York, NY: WH Freeman; 1998.
16. Welch LW, Doineau D, Johnson S, King D. Educational and gender normative data for the Boston Naming Test in a group of older adults. *Brain Lang.* 1996;53:260–266.
17. Beland R, Ska B. Interaction between verbal and gestural language in progressive aphasia: a longitudinal case study. *Brain Lang.* 1992;43:355–385.
18. Rasmussen T, Milner B. The role of early left-brain injury in determining lateralization of cerebral speech functions. In: Dimond S, Blizzard D, eds. *Evolution and Lateralization of the Brain.* New York, NY: New York Academy of Sciences; 1977.
19. Loring DW, Meador K, Lee G, et al. Cerebral language lateralization: evidence from intracarotid amobarbital testing. *Neuropsychologia.* 1990;28:831–838.
20. Harasty J, Double KL, Halliday GM, Kril JJ, McRitchie DA. Language-associated cortical regions are proportionally larger in the female brain. *Arch Neurol.* 1997;54:171–176.