The Discriminant Value of Semiquantitative SPECT Data in Mild Alzheimer's Disease

Denis O'Mahony, John Coffey, John Murphy, Neil O'Hare, David Hamilton, Pat Freyne, J. Bernard Walsh and Davis Coakley

Mercer's Institute for Research on Aging; Department of Diagnostic Imaging and Department of Medical Physics and Bioengineering, St. James's Hospital, Dublin, Ireland

In most semiquantitative SPECT studies, overlap between groups of patients with Alzheimer's disease (AD) and age-matched elderly controls is such that single posterior cortical perfusion measurements lack sensitivity. In the present study, the value of a combination of semiquantitative temporoparietal SPECT parameters was examined. **Methods:** Supratentorial transaxial perfusion measurements were obtained in frontal, anterior temporal, posterior temporoparietal and occipital cortical areas in both hemispheres, in a baseline population of 10 healthy elderly controls and 30 mild to moderately impaired AD patients, as well as in a prospective group of 15 patients with mild cognitive impairment, 12 patients with a diagnosis of probable AD and individual cases of multi-infarct dementia, dementia-frontal type and paranoid psychosis. A linear discriminant function (LDF) was calculated from the baseline subjects' data to classify control and AD subjects individually. **Results:** Highly significant hypoperfusion was noted in both the anterior temporal and posterior temporoparietal regions of interest in the AD group compared with controls, but with significant overlap. Using an LDF incorporating these perfusion measurements in both hemispheres, 10/10 (100%) controls and 26/30 (87%) AD baseline subjects were correctly classified. Using the baseline LDF in the prospective 15 mildly impaired cases, 11/12 new mild AD cases and none of the 3 non-AD cases were classified in the AD group. **Conclusion:** These results support the use of a combination of semiquantitative SPECT perfusion estimates from cortical areas with predictable pathological involvement in AD in a linear discriminant format in the clinical assessment of patients with suspected AD.

Key Words: Alzheimer's disease; SPECT; discriminant function analysis

J Nucl Med 1994; 35:1450–1455

Since the mid 1980s, several qualitative (*1–5*) and semiquantitative (*6–10*) SPECT perfusion studies in Alzheimer disease (AD) patient groups have confirmed that bilateral perfusion deficit in the posterior temporoparietal cortical areas is the "classical" SPECT appearance in AD. However, difficulties arise with regard to the sensitivity of qualitative and single semiquantitative assessments in groups of AD patients. Holman et al. (*11*) have recently noted that the classical posterior temporoparietal perfusion deficit pattern occurs in a minority of AD patients (~27%).

In the semiquantitative studies, the degree of overlap between AD and control groups is such that single temporal or parietal SPECT perfusion parameters are not sufficiently sensitive to be of practical clinical value. Another problem with most of the SPECT studies in AD to date is that most patients had moderate to severe dementia. Thus, an unanswered question regarding the value of SPECT in dementia diagnosis is whether it is sufficiently sensitive in mildly impaired AD patients on a prospective basis. The principal aim of the present study therefore was to evaluate semiquantitative SPECT measurements in less severely impaired patients prospectively, using a discriminant function analysis of SPECT data from the temporoparietal cortex, typically affected in mild AD (*12*).

METHODS

Subjects

Ten healthy control subjects (1 male, 9 females) were recruited from two local active retirement groups. Their mean age was 73.1 yr (s.d. 5.1 yr), and each control subject was free from serious medical illness or long-term medication, specifically psychotropics. None of these subjects had concurrent amnesic or other cognitive symptoms, or first-degree relatives affected by dementia. Their cognitive function was checked using the Mini-Mental State Examination (MMSE) (*13*), each subject attaining scores of ≥28/30. SPECT data from these subjects were compared with data from 30 patients diagnosed as probable AD (pAD) according to NINCDS-ADRDA clinical diagnostic criteria (*14*), which are known to be 80%–90% accurate (*15,16*). In each case the diagnosis of pAD was reserved until 6 mo had elapsed from the time of initial assessment. NINCDS-ADRDA criteria include a CT brain image which was normal or showing atrophy only and no other pathology in each case.

A cerebrovascular etiology was judged to be unlikely in these patients based on Hachinski Ischemic Scale scores of <4/18 (*17*). Dementia severity was graded according to the Clinical Dementia Rating (CDR) system of Hughes et al. (*18*), with 20 pAD patients classed as CDR 1.0 (mild, established dementia), and 10 pAD patients as CDR 2.0 (moderate dementia). Patients were recruited on a consecutive basis from approximately 250 cognitively im-

Received Oct. 28, 1993; revision accepted Mar. 31, 1994.

For correspondence or reprints contact: Dr. Denis O'Mahony, Dept. of Clinical Geratology, Radcliffe Infirmary, Woodstock Rd., Oxford, OX2 6HE, United Kingdom.

TABLE 1
Details of Baseline Control and Alzheimer Disease Patients

	Controls	Alzheimer's
Number (M/F)	10 (1/9)	30 (6/24)
Mean age (s.d.)	73.1 (5.1)	74.0 (4.3)
Mean MMSE (s.d.)*	29.4 (0.7)	17.9 (4.9)

*MMSE out of a total of 30.

paired patients referred to the Alzheimer Assessment Unit at St. James's Hospital over a 2-yr period, in whom a specific clinical diagnosis of dementia type was made after at least 6 mo follow-up in each case. Details of these 40 subjects are depicted in Table 1.

In the second part of the study, SPECT data were obtained in 15 additional patients with very mild (CDR 0.5) or mild (CDR 1) cognitive impairment, of similar age to the 40 subjects in the first part of the study. These patients were recruited prospectively on a consecutive basis from the Alzheimer Assessment Unit, each patient having SPECT imaging as part of their initial diagnostic assessment battery. Clinical details of these patients are contained in Table 2. Among these 15 patients were 12 patients with a diagnosis of pAD and individual cases of cerebrovascular dementia, dementia of the frontal-type and paranoid schizophrenia. Cerebrovascular dementia was diagnosed on the basis of an Hachinski ischemic score of 9/18, typical clinical history and a CT scan showing infarction. Although accepted published clinical criteria for the diagnosis of dementia of the frontal-type (DFT) are not yet available, nevertheless this diagnosis was made on the basis of a clinical history typical of this condition (*19,20*), CT images showing atrophy only and absence of amnesia as a primary presenting feature. Clinical diagnosis remained unchanged at 6-mo follow-up in each case.

SPECT Imaging

Each subject was injected with 740 MBq of ^{99m}Tc-labeled hexamethyl propyleneamine oxime (HMPAO), administered as a bolus through an antecubital vein in a quiet room of constant illumination. Scanning took place 30 min postinjection. SPECT images were obtained using an IGE 400 ACT camera, with acquisition parameters as follows: low-energy, general-purpose collimator, zoom factor 1.6, 64 × 64 matrix, 360° rotation, circular step-and-shoot rotation, 64 views with 30 sec per view. Two-pixel thick transaxial slices in a plane parallel to the supratentorial line were reconstructed, using a Hanning pre-filter with a critical frequency of 0.7 cm^{-1}. The reconstruction was carried out using the backprojection method with a ramp filter. No attenuation correction was applied to the data. The reconstructed slices had a width of 2 pixels. When analyzing the data, the images were first magnified by a factor of 2 in both dimensions, i.e., 128 × 128 display matrix. Square box regions of interest (ROIs) were used to interrogate the data, with a size of 8 × 8 pixels in the magnified images.

Having selected an appropriate color map, ROI boxes were placed on the cortical ribbon of each transaxial slice in frontal, anterior temporal, posterior temporoparietal and occipital sites in both hemispheres in a single supratentorial transaxial plane. This transaxial plane was parallel and 2 pixels superior to the plane defined by a line joining the occipitocerebellar indentation posteriorly and the inferior surface of the frontal lobe anteriorly as viewed on a lateral SPECT image view (Fig. 1). This plane was selected for simplicity in that frontal, anterior temporal, posterior temporoparietal and occipital cortical regions are well-defined, representing known areas of cortical involvement in AD (*12*). ROI placement and average radiotracer count analysis was also simplified using this method, taking less than 10 min in most instances.

Frontal, anterior temporal, posterior temporoparietal and occipital ROIs were defined in both hemispheres in this transaxial plane. The frontal ROI markers were placed on the cortical ribbon in the most anterior aspect of the frontal lobes. The anterior temporal ROIs were placed on the most anterior part of the temporal cortex, as far as could be defined from a series of

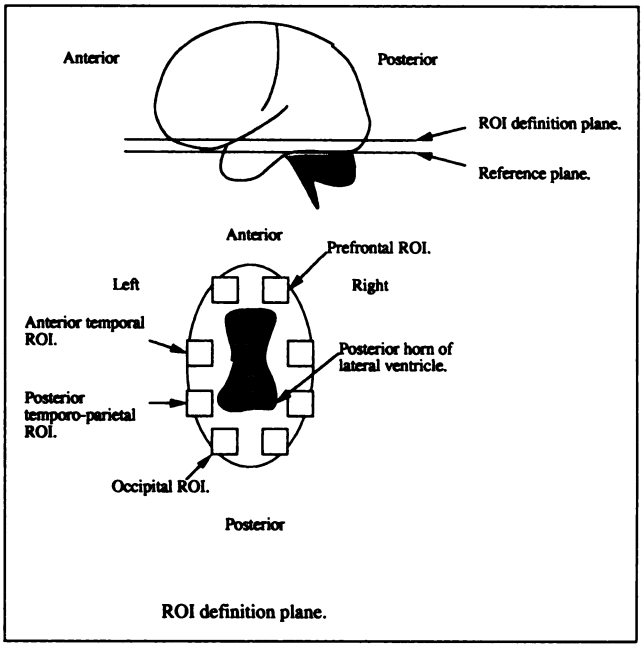

FIGURE 1. Semischematic lateral view of SPECT brain image, with occipitocerebellar-inferior frontal reference plane and ROI plane (upper section), and ROIs in both hemispheres (lower section).

TABLE 2
Details of Prospective Patient Group

Patient (sex)	Age (yr)	MMSE (30)	CDR*	Clinical diagnosis
JC (M)	78	23	1.0	AD
SM (F)	67	22	0.5	AD
ML (F)	68	23	0.5	Multi-infarct dementia
MK (F)	76	27	0.5	AD
JF (M)	77	23	0.5	AD
JB (F)	75	29	0.5	Dementia-frontal type
MA (F)	78	26	0.5	AD
GW (F)	81	24	0.5	AD
MR (F)	69	19	1.0	AD
JM (M)	70	23	0.5	AD
CB (F)	76	15	1.0	AD
RF (F)	77	21	1.0	AD
PF (M)	73	20	1.0	AD
AK (F)	73	25	1.0	AD
FMcC (M)	51	29	0.5	Paranoid psychosis

*CDR = Clinical Dementia Rating.

transaxial slices. The posterior temporoparietal ROIs were placed just lateral to the posterior temporal horns of the lateral ventricles and the occipital ROIs were placed on the most posterior areas of cortex in both hemispheres (Fig. 1). Regions of interest in both hemispheres were symmetrical. Cerebellar ROIs were selected in the middle portion of each cerebellar hemisphere and the average radiotracer count of these two ROIs taken as the reference denominator. The mean radiotracer count per pixel in each of these cortical ROIs was then divided by the mean radiotracer count of both midcerebellar ROIs and expressed as a cortical-to-cerebellar perfusion ratio. The cerebellum was selected as the reference area because of its relative pathological sparing in AD (*12*) and its relative constancy of perfusion.

Statistical Analysis

Data from the "baseline" 40 control and pAD subjects were initially compared using a one-way ANOVA (group × ROI perfusion ratio), to yield control versus pAD comparisons for each of the eight perfusion ratios. Discriminant function analysis was then used to determine which combination of perfusion ratios yielded the optimal correct group classification of subjects. Briefly, discriminant analysis involves the calculation of a linear function comprised of variables which best discriminate between two groups and weighting coefficients, indicating the relative effect of each variable on overall discrimination. This linear discriminant function (LDF) was calculated by a "Minitab®" computer statistical program (State College, PA). The program specified a cut-off point between the two groups and classified individual subjects to either group based on their LDF sum. The LDF was then validated using the so-called "jack-knife" cross-validation procedure (*21*) in which the first baseline subject was excluded from the dataset, a new LDF was developed using the remaining subjects' data and the excluded subject was then classified to one or other group. Next, the program returned to the first subject in the dataset, omitted the second subject's data and repeated the same process. The jack-knife cross-validation continued in this manner until all subjects in the baseline dataset were classified. The power of the LDF to correctly classify further pAD subjects was tested by applying it to the data from the prospective group of 15 mildly impaired subjects. Although not healthy control subjects, the three non-AD cognitively impaired cases were also classified according to their LDF sums.

RESULTS

The results of the ANOVA comparison of the 10 baseline controls and 30 pAD patients are illustrated in Table 3. These show highly significant reductions in the anterior temporal (Ant Temp) and posterior temporoparietal (Post Temp) regional perfusion values in both hemispheres in the pAD group versus controls. No significant frontal or occipital perfusion estimate change between the groups was noted. The greatest degree of difference between the groups occurred with the posterior temporoparietal measurement, but even with this parameter there is a significant degree of group overlap.

The right (R12 and R13) and left (L12 and L13) anterior temporal and posterior temporoparietal cortical-to-cerebellar perfusion ratios and the LDF sums are illustrated in Table 4. The cut-off between control and pAD groups was 2.90. With this cut-off, 10/10 (100%) controls and 26/30 (87%) pAD baseline subjects were correctly classified. The misclassified pAD patients included three CDR 1 (mild dementia) patients and one CDR 2 (moderate dementia) patient. The jack-knife cross-validation procedure correctly classified 10/10 controls (100%) and 24/30 (80%) pAD cases. Classification of the 15 prospective cognitively impaired patients (detailed in Table 2) using the same cut-off of 2.90 was correct in 11/12 mild pAD cases. None of the three non-AD cases was classified to the pAD group (Table 5).

TABLE 3
Baseline Group Comparison of Individual SPECT-Derived Cortical-to-Cerebellar Perfusion Ratios (Group × ROI ANOVA)

	Group mean cortical-to-cerebellar perfusion ratio		One-way ANOVA
SPECT ROI	Controls (n = 10)	Alzheimer's (n = 30)	p-value
R. frontal	0.70 (0.07)	0.69 (0.08)	0.72
R. ant. temp.	0.78 (0.04)	0.71 (0.06)	<0.001
R. post. T-P	0.83 (0.05)	0.75 (0.07)	<0.005
R. occipital	0.93 (0.05)	0.90 (0.09)	0.34
L. frontal	0.73 (0.08)	0.70 (0.08)	0.31
L. ant. temp.	0.79 (0.06)	0.72 (0.05)	<0.001
L. post. T-P	0.90 (0.05)	0.79 (0.06)	<0.0001
L. occipital	0.94 (0.06)	0.90 (0.08)	0.11

Ant. temp. = anterior temporal; and post. T-P = posterior temporoparietal.

DISCUSSION

The principal findings of this study are: (1) although temporoparietal hypoperfusion is a constant feature of the mild and moderate stages of AD, use of single SPECT-derived temporoparietal perfusion measurements is not sufficiently sensitive to be of diagnostic value; and (2) simultaneous consideration of anterior temporal and posterior temporoparietal cortical perfusion measurements in a linear discriminant function format is a sensitive and specific means of discriminating individual pAD patients from controls. Temporoparietal hypoperfusion is consistent with the known distribution of cortical plaque/tangle damage from surveys of histopathological change in AD (*12*), and it is generally accepted that the earliest affected neocortical areas in AD are the hippocampus/medial temporal and inferior temporoparietal regions (*22*).

Some authors have suggested that the disease begins in the entorhinal cortex and spreads according to reciprocal innervation pathways to involve the hippocampus and subsequently the inferior and lateral temporoparietal cortical mantle as the disease advances (*12*). At present, the spatial resolution of SPECT systems does not allow accurate qualitative or semiquantitative perfusion assessments of the hippocampus in isolation. Thus, the earliest involved cortical area which is expected to show abnormalities on SPECT imaging is the infero-lateral temporoparietal area.

TABLE 4

Details of Baseline Control and Alzheimer Patients' Right and Left Hemisphere Anterior Temporal and Posterior Temporoparietal Cortical-to-Cerebellar Perfusion Ratios with Linear Discriminant Function Scores*

Group	Patient	R12	R13	L12	L13	R12 × 1.283	+	R13 × 0.138	+	L12 × −0.208	+	L13 × 2.373	=	LDF sum
CONT	SW	0.754	0.807	0.728	0.850	0.967		0.111		−0.151		2.017		2.944
CONT	MO'R	0.739	0.817	0.826	0.910	0.948		0.113		−0.172		2.159		3.049
CONT	JK	0.781	0.808	0.789	0.85	1.002		0.112		−0.164		2.017		2.966
CONT	PS	0.827	0.786	0.765	0.857	1.061		0.108		−0.159		2.034		3.044
CONT	MH	0.786	0.922	0.747	0.912	1.008		0.127		−0.155		2.164		3.144
CONT	AB	0.704	0.867	0.800	0.967	0.903		0.120		−0.166		2.295		3.151
CONT	NM	0.791	0.806	0.705	0.852	1.015		0.111		−0.147		2.022		3.001
CONT	BM	0.795	0.821	0.846	0.974	1.02		0.113		−0.176		2.311		3.269
CONT	MG	0.771	0.819	0.795	0.867	0.989		0.113		−0.165		2.057		2.994
CONT	KS	0.853	0.922	0.914	0.991	1.094		0.127		−0.19		2.352		3.383
AD	MO'B	0.778	0.764	0.765	0.753	0.998		0.105		−0.159		1.787		2.731
AD	CE	0.770	0.750	0.600	0.714	0.988		0.104		−0.125		1.694		2.661
AD	TS	0.642	0.717	0.694	0.838	0.824		0.099		−0.144		1.989		2.767
AD	ED	0.629	0.702	0.685	0.795	0.807		0.097		−0.142		1.887		2.648
AD	MS	0.766	0.849	0.782	0.819	0.983		0.117		−0.163		1.943		2.881
AD	MMcG	0.679	0.717	0.667	0.641	0.871		0.099		−0.139		1.521		2.352
AD	RM	0.678	0.827	0.667	0.862	0.870		0.114		−0.139		2.046		2.891
AD	TC	0.694	0.746	0.732	0.760	0.890		0.103		−0.152		1.803		2.645
AD	MD	0.750	0.800	0.700	0.667	0.962		0.110		−0.146		1.583		2.510
AD	MG	0.647	0.709	0.709	0.785	0.830		0.098		−0.147		1.863		2.643
AD	TMcG	0.638	0.697	0.691	0.743	0.819		0.096		−0.144		1.763		2.534
AD	EA	0.850	0.750	0.838	0.887	1.091		0.104		−0.174		2.106		3.126
AD	MG	0.746	0.804	0.717	0.819	0.957		0.111		−0.149		1.943		2.862
AD	EH	0.825	0.820	0.730	0.834	1.058		0.113		−0.152		1.979		2.999
AD	CW	0.696	0.674	0.739	0.783	0.893		0.093		−0.154		1.858		2.690
AD	MP	0.714	0.548	0.690	0.786	0.916		0.076		−0.144		1.865		2.713
AD	MMcS	0.634	0.683	0.732	0.829	0.813		0.094		−0.152		1.967		2.723
AD	KF	0.758	0.774	0.774	0.719	0.973		0.107		−0.161		1.706		2.625
AD	MC	0.709	0.854	0.825	0.845	0.910		0.118		−0.172		2.005		2.861
AD	JG	0.800	0.800	0.720	0.693	1.026		0.110		−0.150		1.644		2.632
AD	VF	0.678	0.797	0.763	0.831	0.870		0.110		−0.159		1.972		2.793
AD	AO'L	0.674	0.716	0.684	0.789	0.865		0.099		−0.142		1.872		2.694
AD	FF	0.685	0.713	0.720	0.776	0.879		0.098		−0.150		1.841		2.669
AD	JL	0.629	0.664	0.622	0.701	0.807		0.092		−0.129		1.663		2.433
AD	JM	0.645	0.704	0.704	0.800	0.828		0.097		−0.146		1.898		2.677
AD	KB	0.747	0.871	0.730	0.862	0.958		0.120		−0.152		2.046		2.972
AD	GQ	0.794	0.867	0.658	0.793	1.019		0.120		−0.137		1.882		2.883
AD	JG	0.714	0.714	0.738	0.786	0.916		0.099		−0.154		1.865		2.726
AD	MY	0.698	0.830	0.811	0.924	0.896		0.115		−0.169		2.193		3.034

*Scores <2.90 classify subjects to the Alzheimer group; scores >2.90 classify subjects to the control group.
CONT = control; 12 = anterior temporal; and 13 = posterior temporo-parietal.

The hypoperfusion noted in this area in both hemispheres (left more than right) in pAD patients is unlikely to result simply from exaggerated cortical atrophy. A striking degree of local atrophy was not evident in the transaxial CT images in the present study. Also, existing data from PET studies in patients with early AD indicate that neuronal functional disturbances (with associated hypoperfusion) predates atrophy (*23*).

Most published studies attempting to validate SPECT in correctly identifying AD cases have included patients with at least moderately severe dementia. At this stage of dementia, the diagnosis is usually clearcut so that functional neuroimaging with SPECT has little further to offer in terms of clinical clarification or management. If SPECT is to be of practical clinical value, it must be able to discriminate very mild (CDR 0.5) and mild (CDR 1.0) forms of AD from normal aging, once macrostructural lesions have been excluded by means of CT or MRI. The high degree of correct classification of the prospective mildly impaired pAD patients (11/12) with linear discriminant function analysis in this study indicates that SPECT imaging may be useful in the assessment of early cognitive impairment. It is also pertinent that all of the CDR 0.5 (very mild dementia) AD cases in the prospective patient group were correctly classified. Each of these six patients has been followed up for periods of between 6–15 mo from the time of initial assessment. Deterioration to CDR 1.0 status has been noted in four of the six patients.

TABLE 5

Details of 15 Prospective Mildly Impaired Patients' Right and Left Hemisphere Anterior Temporal and Posterior Temporoparietal Cortical-to-Cerebellar Perfusion Ratios and Linear Discriminant Function Scores*

Diagnosis	ID	R12	R13	L12	L13	R12 × 1.283	+	R13 × 0.138	+	L12 × −0.208	+	L13 × 2.373	=	LDF sum
AD	JC	0.662	0.715	0.702	0.754	0.849		0.099		−0.146		1.789		2.591
AD	SM	0.715	0.818	0.876	0.708	0.917		0.113		−0.182		1.680		2.528
MID	ML	0.708	0.754	0.712	0.874	0.909		0.104		−0.148		2.075		2.940
AD	MK	0.690	0.739	0.690	0.721	0.885		0.102		−0.144		1.711		2.554
AD	JF	0.646	0.737	0.720	0.635	0.829		0.102		−0.149		1.507		2.289
DFT	JB	0.717	0.852	0.776	0.887	0.920		0.118		−0.161		2.183		3.060
AD	MA	0.672	0.781	0.639	0.770	0.862		0.108		−0.133		1.827		2.664
AD	GW	0.770	0.858	0.765	0.744	0.988		0.118		−0.159		1.765		2.713
AD	MR	0.805	0.798	0.829	0.825	1.033		0.110		−0.172		1.958		2.929
AD	JM	0.647	0.695	0.734	0.824	0.830		0.096		−0.153		1.955		2.728
AD	CB	0.705	0.667	0.735	0.688	0.905		0.092		−0.153		1.633		2.477
AD	RF	0.707	0.824	0.850	0.858	0.907		0.114		−0.177		2.036		2.880
AD	PF	0.678	0.797	0.704	0.746	0.870		0.110		−0.146		1.770		2.604
AD	AK	0.693	0.853	0.615	0.442	0.889		0.118		−0.128		1.049		1.928
P. Psych	FMcC	0.765	0.878	0.851	0.859	0.981		0.121		−0.177		2.038		2.963

*LDF sums <2.90 classify subjects to the AD group.

12 = anterior temporal; 13 = posterior temporo-parietal; MID = multi-infarct dementia; DFT = dementia-frontal-type; and P. Psych. = paranoid psychosis.

In the original description of the CDR scale, Hughes et al. (*18*) referred to the CDR 0.5 descriptor as "questionable dementia." However, follow-up evaluation of a cohort of 16 CDR 0.5 patients by Rubin et al. (*24*) confirmed definite progression in 11 of these 16 patients. These authors suggest that CDR 0.5 status represents incipient AD in most cases, and that patients of this category should be referred to as having "very mild dementia of the Alzheimer type," instead of "questionable dementia." The question of detection of preclinical AD (in first-degree relatives of AD patients, for example) using similar multivariate statistical analysis of SPECT data has yet to be addressed.

Our results indicate that assessment of semiquantitative SPECT perfusion parameters in a discriminant function format may be a useful means of differentiating early AD patients from normal elderly. Our study has a number of limitations, namely (1) the relatively small number of baseline control and prospective subjects; (2) the fact that dementia differential diagnosis awaits autopsy confirmation; and (3) linear discriminant functions for differentiating dementia subtypes are not yet available due to limited numbers of non-Alzheimer dementia patients. However, we believe that multivariate statistical methods such as discriminant analysis may provide a more appropriate technique of semiquantitative SPECT data analysis in differentiating normal elderly from mild Alzheimer's disease and possibly one type of dementing disorder from another.

ACKNOWLEDGMENTS

The authors thank Nurse Irene Bruce (Mercer's Institute, St. James's Hospital), Angela Montgomery, Helen Ryder and Pauline Malone (Department of Diagnostic Imaging, St. James's Hospital), and Eamon Mullins (Dept. Statistics, Trinity College, Dublin) in the present study. The work was supported financially by the Mercer's Fund and by the Health Research Board of Ireland.

REFERENCES

1. Johnson KA, Mueller ST, Walshe TM, English RJ, Holman BL. Cerebral perfusion imaging in Alzheimer's disease. *Arch Neurol* 1987;44:165–168.
2. Jagust WJ, Budinger TF, Reed BR. The diagnosis of dementia with single photon emission computed tomography. *Arch Neurol* 1987;44:258–262.
3. Neary D, Snowden JS, Shields RA, et al. Single photon emission computed tomography using ^{99m}Tc-HMPAO in the investigation of dementia. *J Neurol Neurosurg Psychiatry* 1987;50:1101–1109.
4. Gemmell HG, Sharp PF, Besson JA, et al. Differential diagnosis of dementia using the cerebral blood flow agent ^{99m}Tc-HMPAO: a SPECT study. *J Comput Assist Tomogr* 1987;11:398–402.
5. Podreka I, Suess E, Goldenberg G, et al. Initial experience with technetium-99m-HMPAO brain SPECT. *J Nucl Med* 1987;28:1657–1666.
6. Perani D, Di Piero V, Vallar G, et al. Technetium-99m-HMPAO SPECT study of regional cerebral perfusion in early Alzheimer's disease. *J Nucl Med* 1988;29:1507–1514.
7. Burns A, Philpott MP, Costa DC, Ell PJ, Levy R. The investigation of Alzheimer's disease with single photon emission tomography. *J Neurol Neurosurg Psychiatry* 1989;52:248–253.
8. Goldenberg G, Podreka I, Suess E, Deeke L. The cerebral localization of neuropsychological impairment in Alzheimer's disease: a SPECT study. *J Neurol* 1989;236:131–138.
9. Hunter R, Mcluskie R, Wyper D, et al. The pattern of function-related regional cerebral blood flow investigated by single photon emission tomography with ^{99m}Tc-HMPAO in patients with presenile Alzheimer's disease and Korsakoff's psychosis. *Psychol Med* 1989;19:847–855.
10. Montaldi D, Brooks D, McColl J, et al. Measurement of regional cerebral blood flow and cognitive performance in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1990;53:33–38.
11. Holman LB, Johnson KA, Gerada B, Carvalho PA, Satlin A. The scintigraphic appearance of Alzheimer's disease: a prospective study using technetium-99m-HMPAO SPECT. *J Nucl Med* 1992;33:181–185.
12. Pearson R, Powell T. The neuroanatomy of Alzheimer's disease. *Rev Neurosci* 1989;2:101–122.
13. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state:" a practical method for grading the mental state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198.
14. Mckhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzhei-

mer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology* 1984;34:939–944.
15. Joachim CL, Morris JH, Selkoe DJ. Clinically diagnosed Alzheimer's disease: autopsy results in 150 cases. *Ann Neurol* 1988;24:50–56.
16. Tierney MC, Fisher RH, Lewis AJ, et al. The NINCDS-ADRDA work group criteria for the clinical diagnosis of probable Alzheimer's disease: a clinicopathological study of 57 cases. *Neurology* 1988;38:359–364.
17. Hachinski VC, Illiff LD, Zilhka E, et al. Cerebral blood flow in dementia. *Arch Neurol* 1975;32:632–637.
18. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry* 1982;140:566–572.
19. Orrell MW. Dementia of frontal lobe type (Editorial). *Psychol Med* 1991; 21:553–556.
20. Neary D. Non-Alzheimer's disease forms of cerebral atrophy [Editorial]. *J Neurol Neurosurg Psychiatry* 1990;53:929–931.
21. Afifi AA, Clark V. Discriminant analysis. In: *Computer-aided multivariate analysis.* New York: Von Nostrand Company; 1984:246–286.
22. Tomlinson B. Aging and the dementias. In: Adams JH, Duchen LW, Eds. *Greenfield's neuropathology*, fifth edition. London: Edward Arnold; 1992: 1284–1410.
23. Burns A, Tune L, Steele C, Folstein M. Positron emission tomography in dementia: a clinical review. *Int J Geriatr Psychiatry* 1989;4:67–72.
24. Rubin EH, Morris JC, Grant EA, Vendegna T. Very mild senile dementia of the Alzheimer type. I. Clinical assessment. *Arch Neurol* 1989;46:379–382.

EDITORIAL

Discriminant Function Analysis: Toward a More Rigorous Approach to SPECT Interpretation

Perfusion brain imaging using SPECT continues to be developed as a viable means by which to detect and assess various forms of dementia, especially Alzheimer's disease (AD) (*1–3*). Using SPECT brain functional imaging, investigators have studied Alzheimer's disease more than any other dementia; this correlates with the high prevalence of the disease in the population (*4,5*). Dementia is associated with numerous conditions, with AD and vascular disease being the most prevalent. In a recent clinical study involving 494 unselected 85-yr-olds, one-third were found to have dementia: 42% due to AD and 47% due to vascular ischemia (*6*). Another study found a 10.5% incidence of moderate to severe dementia in 80 to 84-yr-olds and 20.8% in 85 to 89-yr-olds (*7*). Annual healthcare expenses related to AD are estimated to exceed $50 billion (*8*). Because a number of the diseases related to dementia, including vascular disease, are treatable, it is important to differentiate as early as possible between AD and other dementia-related diseases. Since an effective treatment for AD remains to be found, diagnostic imaging is largely an exclusionary process (*9*) involving the use of computed tomography (CT) or magnetic resonance imaging (MRI).

One important advantage that brain functional imaging with SPECT has over MRI and CT for the early diagnosis of AD is its capacity to detect deterioration in brain function. Standard MRI and CT can only detect the anatomical and structural changes related to AD, which are the late-stage manifestations of a gradual deterioration process (*10–12*). Functional MRI is not yet as accurate as SPECT in the diagnosis of AD.

Earlier studies using PET scanning with [^{18}F]FDG in AD patients demonstrated cortical metabolic deficits, particularly in the posterior temperoparietal regions of both cerebral hemispheres (*13*). Using both ^{123}I-IMP and ^{99m}Tc-HMPAO SPECT, investigators have found perfusion defects which match the metabolic abnormalities seen with PET (*14–16*). While other perfusion patterns are found in AD patients, the most commonly identified pattern is bilateral posterior temperoparietal perfusion defects, often in an asymmetrical pattern. Investigators have reported a likelihood of AD in 84% of patients in whom this specific localization of degeneration is seen (*17–19*). This SPECT pattern is found in approximately 65% of all AD patients. If Parkinson's disease has been excluded clinically, the likelihood of AD increases to over 90% when this pattern is present (*17*). Perfusion defects in AD patients have also been seen in the frontal, medial temporal and anterolateral cortex, but unless bilateral posterior temperoparietal defects are present, the patterns are not specific for AD (*18*).

In this issue, O'Mahony et al. applied discriminant analysis to semiquantitative SPECT datasets in patients with mild AD. This important study includes a cohort of patients with very mild dementia (CDR 0.5), demonstrating that, with discriminant analysis, it is possible to identify perfusion abnormalities in potentially very mild disease. As important as it is to extend the work to patients classified as CDR 0.5, it is important to remember that only a fraction of patients so classified turn out to have AD. It is only by looking at a large cohort of such patients and following them for a long time that it is possible to determine the accuracy of the method. Nevertheless it is very important to determine that SPECT brain perfusion imaging is sensitive enough to detect perfusion abnormalities in this group of patients. Extension of this work to a larger group of patients might result in the identification of brain perfusion SPECT as a primary screening tool in early AD.

The use of discriminant analysis in this study avoids the subjectivity of visual interpretation and incorporates the entire scintigraphic pattern in de-

Received May 4, 1994; accepted June 13, 1994.
For correspondence or reprints contact: Thomas C. Hill, MD, Division of Nuclear Medicine, New England Deaconess Hospital, 185 Pilgrim Road, Boston, MA 02115.