Discriminative Use of SPECT in Frontal Lobe-Type Dementia Versus (Senile) Dementia of the Alzheimer's Type

Barbara A. Pickut, Jos Saerens, Peter Mariën, Fons Borggreve, Johan Goeman, Johan Vandevivere, An Vervaet, Rudi Dierckx and Peter P. De Deyn

Memory Clinic, Department of Neurology and Nuclear Medicine, General Hospital Middelheim, and Department of Neurology, Laboratory of Neurochemistry and Behavior, Born-Bunge Foundation, University of Antwerp and University Hospital of Ghent, Belgium

Dementia of the Alzheimer's type [(S)DAT] and dementia with frontal features (FLD) are nosological entities with different prognoses and presumed pathophysiology. There is a need for noninvasive differential diagnostic tools. To evaluate whether SPECT perfusion imaging could discriminate between these neurodegenerative disorders, we performed a comparative study. **Methods:** SPECT scans using ^{99m}Tc-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO) of 21 patients with FLD were compared with those obtained in a group of 19 age- and severity-matched patients suffering from (S)DAT. Brain SPECT perfusion deficits were scored by visual qualitative analysis with respect to location, lateralization and severity. A total severity score of cerebral hypoperfusion (maximal value = 18) was calculated by adding all severity scores (scored between 0 and 3; 0 = no perfusion deficit; 1 = 13%–30% hypoperfusion; 2 = 30%–50% hypoperfusion and 3 = >50% hypoperfusion including breaching of the cortex) for right and left frontal, parietal and temporal lobes. Moreover, bifrontal hypoperfusion (F_s) was scored, yielding a value between 0 and 6 by adding the two frontal severity scores. **Results:** No significant correlation was found between MMSE scores and total severity scores on SPECT. A statistically significant correlation was found between the Middelheim frontality score and frontal severity score. Statistically more significant bilateral hypoperfusion of the parietal lobes was found in the (S)DAT group. Conversely, bifrontal hypoperfusion was found more in the FLD group. Stepwise logistic regression analysis identified the severity of bifrontal hypoperfusion as the most significant contributing parameter to correctly classifying (S)DAT versus FLD on SPECT. The probability of predicting (S)DAT based on the SPECT scan is calculated with the following formula:

$$p(DAT) = 1/[1 + e^{-(1.1-0.661\times Fs)}].$$

Using this equation, a value above 0.5 was predictive for (S)DAT and a calculated value under 0.5 was predictive for FLD. Using this model, 81% of the FLD group and 74% of the (S)DAT were correctly classified. **Conclusion:** Technetium-99m-HMPAO SPECT may help in discriminating FLD from (S)DAT. Bifrontal hypoperfusion was found to be the most powerful predictor of clinical classification. Further validation of the presented logistic regression model is warranted.

Key Words: dementia; Alzheimer's disease; brain perfusion; SPECT

J Nucl Med 1997; 38:929–934

Neurodegenerative diseases of the brain are complex and inter-related illnesses that may share important behavioral and pathologic characteristics. The differential diagnosis may present difficulties in some cases and therefore research continues seeking new diagnostic tools. Unfortunately, our knowledge of these diseases is based largely on postmortem studies mostly at the end-stage of the diseases. Functional imaging provides a measure of the vital functions of the brain such as microperfusion and by inference local metabolism during life and may help address the clinician's concerns.

The focus of this article is SPECT differentiation of two important forms of neurodegenerative dementia: the most frequent form being senile dementia of the Alzheimer type and the less predominant being dementia with frontal lobe features (FLD).

FLD has been recognized as a variant of progressive non-Alzheimer dementia and is a relatively new concept. This disease was once thought to be synonymous with Pick's dementia. Clinical, regional cerebral blood flow and neuropathologic data suggest that FLD is a member of a larger clinico-pathological syndrome related with respect to the site of cortical involvement. The etiology of FLD is still unknown. A positive family history for the disease was reported in 60% of a group of 30 Swedish patients (*1*). Frontal lobe degeneration of the non-Alzheimer's type follows SDAT as the second most common primary degenerative dementia. It has been suggested that 8% (*1*) to 20% (*2*) of early-onset dementia may be attributed to this variant.

The term FLD was launched in 1987 (*3*). This entity is characterized by a neuropsychiatric syndrome, a nonspecific type of histo-pathological picture (*4,5*) and a typical pattern of reduced regional cerebral blood flow (*6*). Patients generally begin to exhibit symptoms in middle age (*7*).

The neuropsychiatric syndrome of FLD has been described as follows. A progressive increment of a variety of neurobehavioral changes form a highly characteristic phenomenon. At the early onset of the disorder, disturbances of social skills, inadequate affect, apathy, depressed mood, hypomania, sloppiness and impaired judgement constitute frequently reported behavioral anomalies. Impulsivity, disinhibition, emotional restlessness, hyperorality and psychotic changes usually appear in a somewhat later stage of the disease, while rigid behavior, a tendency to simplicity in activities, oral dietary changes and perseverations reflect already marked character alterations. In addition to prominent personality changes, the disorder is typically characterized by a progressive loss of expressive speech initiation (verbal inhibition, adynamia), with verbal stereotypes often evolving to echolalia and frontal mutism syndrome. In contrast to (S)DAT, in which behavioral changes mostly either occur only at a late stage or as a secondary reaction to cognitive failure, the neurocognitive dysfunction of memory, praxis, gnosis, temporal and spatial orientation remain comparatively longer preserved in FLD.

The neuropathological presentation of FLD involves no

Received Apr. 8, 1996; revision accepted Sept. 19, 1996.

For correspondence or reprints contact: P.P. De Deyn, MD, PhD, MMPR, Department of Neurology, General Hospital Middelheim, University of Antwerp, Lindendreef 1, 2020 Antwerp, Belgium.

distinctive subcellular dysmorphic features such as neurofibrillary tangles, Pick bodies, Lewy bodies or ballooned cells (*8*). FLD is a primary cortical disorder with degeneration of the superficial layers of the frontal and anterior temporal cortex (lamina I-III) with mild gliosis and microvacuolation.

Finally, it has been suggested that a typical pattern of frontally reduced regional cerebral blood flow might further characterize FLD. In early studies with ^{133}Xe, SPECT is reported to give highly characteristic results in patients suspected to have FLD (*9–12*). Patients with FLD were found to have focal frontal or frontotemporal blood flow reductions involving both hemispheres.

This pattern of reduced flow in the frontal lobes, however, is not specific. Such an abnormality can be found in Pick's disease, Creutzfeldt-Jakob's disease, and in some cases of Alzheimer's disease (*4*). Low frontal flow has also been described in schizophrenia and in toxic encephalopathy (alcohol, organic solvents) (*13*) as well as in depression (*14*). Moreover, HIV-infected demented patients are also reported to have frontal hypoperfusion (*15,16*). Also, dementias associated with motor neuron disease and primary progressive aphasia yield SPECT scans with fronto-temporal hypoperfusion, possibly related to regional atrophies (*17*). Moretti et al. (*18*) assessed cortical perfusion in patients with normal pressure hydrocephalus (NPH) and found a frontal hypoactive pattern not attributable to focal anatomic changes.

We studied brain perfusion in two clinically defined populations: one consisting of 21 patients suffering from FLD and an other group consisting of 19 age- and severity-matched (S)DAT patients to ascertain if there were characteristics that could support the clinical diagnosis and further demonstrate pathological differences.

MATERIALS AND METHODS

Patients

All 40 patients selected for this study underwent a general physical examination, routine blood screening, neuroimaging consisting of CT and/or MRI to exclude concurrent pathology (vascular dementia, atrophy, tumors, focal or more than age-associated atrophy), BEAM, EEG and an extensive neuropsychological examination as routinely performed in the differential diagnostic work-up in our institution. Vascular dementia was excluded on clinical grounds and morphological neuroimaging conforms with the DSM IV criteria. All 40 patients initially underwent a battery of tests consisting of the Mini Mental State Examination (MMSE), the Hierarchic Dementia Scale (*19*) and Raven's Colored or standard Progressive Matrices. The patients with a presenile onset, additionally underwent Wechsler Adult Intelligence Scale, Wechsler Memory Scale, Rey's 15 word list of auditory learning, Rey-Osterrieth figure, Benton's visual form discrimination, Benton's judgement of line orientation, Boston Naming Test, Wisconsin Card Sorting Test and a verbal fluency task consisting of a 1-min semantic category generation (animals, transportation, vegetables, clothing) and a 2-min phonemic word generation task starting with the phonemes F, A and S. In addition, the MFS (Middelheim Frontality Score) was determined for all patients. This score is indicative of frontal lobe features and is obtained by adding the scores obtained on 10 items. Each item is scored either 0 (=absent) or 1 (=present) based on (hetero)anamnesis and/or clinical observation yielding a total maximal score of 10. The 10 items scored are: initially comparatively spared memory and spatial abilities (score 1); personality and behavioral changes: loss of insight and judgement (score 2), disinhibition (score 3), dietary hyperactivity (score 4), changes in sexual behavior (score 5), stereotyped behavior (score 6), impaired control of emotions (score 7), aspontaneity (score 8); speech disturbances such as stereotyped phrases, logorrhea, echolalia, mutism, amimia (score 9) and restlessness (score 10).

Twenty-one patients clinically diagnosed with FLD were selected from the records of our Memory Clinic, amounting to 7.3% of the newly investigated patients for cognitive deterioration between 1992 and 1995. For this study, age- and severity-matched FLD (n = 21) and (S)DAT (n = 19) groups were considered. The diagnosis of probable SDAT was based on National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria (NINCDS/ADRDA) (*20*). The patients also fulfilled the DSM IV-criteria. Since the distinctive diagnostic features of SDAT and FLD are from the present descriptions more qualitative nature than quantitative, severity matching was restricted to cognitive failure only. As a first approximation, we selected the MMSE for this purpose because of its widespread utilization and ease of use in nonspecialized settings. Patient age in both groups was 70 ± 9 (mean± s.d.) years; MMSE score in the FLD group was 15.4 ± 4.9 (mean ± s.d.) and 14.8 ± 5.3 (mean ± s.d.) in the (S)DAT group.

SPECT Acquisition and Analysis

All 40 patients underwent ^{99m}Tc-HMPAO SPECT studies. HMPAO (20 mCi, 740 MBq), prepared according to the manufacturer's instructions, was administered using a previously inserted and fixed butterfly needle while the patient laid on bed in a quiet room with indirect neon lighting, eyes open and ears unplugged. Four point sources were fixed along the orbitomeatal axis as reference for later reorientation of the transverse slices.

Data acquistion was started 20 min postinjection, using a three-detector system (Triad 88, Trionix Research Laboratory, Twinsburg, OH) equipped with lead high-resolution fanbeam collimators. Data were collected for 40 projections per camera head (3° steps, 40 sec per projection, 128 × 64 matrix, pixel size 3.6 mm). Projection images were smoothed and reconstructed in a 64 × 64 matrix, using a Butterworth filter with a high cutoff frequency and roll-off of 5. The slices were reoriented parallel to the orbitomeatal axis.

The SPECT images were all read by two physicians (BAP and RD) experienced in nuclear medicine and neurology. Consensus reading was performed. The physicians were unaware of the type and severity of cognitive impairment of the patient studied. Images were assessed qualitatively by visual interpretation on shades of color in cortical regions. The monitor display format had a 10 component color scale with cerebellum, visual cortex and basal ganglia representing the maximum of reconstructed activity. Each patient's dataset was normalized individually to the mean cerebellar pixel values.

Brain SPECT perfusion deficits were scored by visual qualitative analysis with respect to location: frontal, parietal, temporal and occipital; lateralization: left and or right; and severity score:

0 = normal (no perfusion deficit)
1 = slight (13%–30%)
2 = moderate (30%–50%)
3 = severe (>50%, including breaching of the cortex).

For bilateral lesions, the adjacent cortex was used as a guideline.

A total severity score was calculated by adding all severity scores for right and left frontal, parietal and temporal lobes, yielding a theoretical maximum value of 18 (6 × 3). In addition, a severity score of bifrontal hypoperfusion (Fs) was calculated. Fs was obtained by adding the severity scores (minimal 0 to maximal 3) of both frontal lobes, yielding a minimal value of 0 for normal

TABLE 1
MMSE, MFS and SPECT Findings in Patients with Dementia

Patient no.	MMSE	MFS	Holman score	Temporal hypoperfusion*		Parietal hypoperfusion*		Frontal hypoperfusion*		Clinical diagnosis
				Left	Right	Left	Right	Left	Right	
1	5	5	D	0	1	0	1	0	0	DAT
2	16	2	G	1	0	1	1	1	0	DAT
3	16	0	C	2	0	2	0	2	2	DAT
4	10	4	C	3	2	2	1	2	2	DAT
5	15	1	C	2	2	2	2	1	1	DAT
6	7	2	B	2	3	1	2	0	0	DAT
7	7	2	C	1	2	1	2	0	1	DAT
8	21	0	C	2	3	1	2	1	0	DAT
9	21	1	C	2	3	1	2	2	2	DAT
10	10	0	B	2	1	1	1	0	0	DAT
11	14	3	D	2	0	1	0	0	0	DAT
12	15	4	C	2	1	2	1	1	0	DAT
13	24	3	C	1	2	1	0	0	1	DAT
14	18	4	C	1	2	1	2	0	1	DAT
15	16	3	C	2	0	1	1	0	0	DAT
16	21	1	C	0	0	1	1	1	0	DAT
17	19	0	C	0	1	1	2	0	0	DAT
18	11	4	D	0	0	1	0	1	1	DAT
19	16	0	D	2	0	1	0	0	1	DAT
20	20	7	D	1	0	1	0	2	1	FLD
21	14	7	C	2	3	2	3	1	2	FLD
22	14	7	D	0	0	0	1	0	0	FLD
23	16	8	C	2	1	2	0	2	1	FLD
24	18	5	D	0	2	0	0	1	2	FLD
25	12	5	E	0	0	0	0	2	1	FLD
26	5	5	C	2	1	1	0	2	1	FLD
27	8	3	D	1	0	2	0	0	0	FLD
28	20	6	E	0	0	0	0	1	1	FLD
29	26	3	B	0	2	1	2	0	0	FLD
30	12	4	C	2	1	1	1	1	1	FLD
31	18	5	D	2	0	1	0	2	1	FLD
32	20	7	D	2	0	1	0	2	1	FLD
33	13	6	D	2	0	1	0	2	2	FLD
34	20	6	C	3	2	2	1	2	1	FLD
35	13	2	D	0	1	0	2	1	2	FLD
36	20	1	D	0	0	2	0	1	2	FLD
37	16	6	C	1	2	1	2	0	2	FLD
38	17	7	C	1	0	1	1	1	1	FLD
39	12	7	D	0	2	1	1	2	2	FLD
40	10	7	D	0	2	0	1	0	1	FLD

*Severity score; 0 = normal; 1 = slight (13%–30%); 2 = moderate (30%–50%); and 3 = severe (>50%). MMSE = Mini Mental State Examination Score; MFS = Middelheim Frontality Score; SDAT = (Senile) dementia of the Alzheimer's type; FLD = frontal lobe type dementia. A = normal; B = bilateral posterior temporal and/or parietal cortex defects; C = bilateral posterior temporal and/or parietal cortex defects with additional defects; D = unilateral posterior temporal and/or parietal cortex defects with or without additional defects; E = frontal cortex defects only; F = other large (>7 cm) defects; G = multiple small (≤7 cm) cortical defects.

bifrontal perfusion and a maximal score of 6 for severe bifrontal hypoperfusion. When there was a bilateral anterior-posterior gradient, the cerebellum was used as a reference with a minimal index of 65%.

In addition, images were interpreted according to the method of Holman (*21*) into the following perfusion patterns:

A: Normal
B: Bilateral posterior temporal and/or parietal cortex defects.
C: Bilateral posterior temporal and/or parietal cortex defects with additional defects.
D: Unilateral posterior temporal and/or parietal cortex defects with or without additional defects.
E: Frontal cortex defects only
F: Other large (>7 cm) defects
G: Multiple small (≤7 cm) cortical defects

Data Analysis

Statistical analysis of the data was performed using the Mann-Whitney two-sample test and Spearman's rank correlation. Stepwise logistic regression was performed to determine independent discriminators of FLD and (S)DAT. It enables us to predict the probability of a particular outcome in relation to several prognostic variables. A p value of < 0.05 (two-sided) was considered significant.

RESULTS

MMSE score, Middelheim Frontality score, classification according to Holman, temporal, parietal and frontal hypoperfusion on the right and on the left side, as well as the clinical diagnosis of all patients involved are listed in Table 1. There were no regions of occipital hypoperfusion with more than 13%

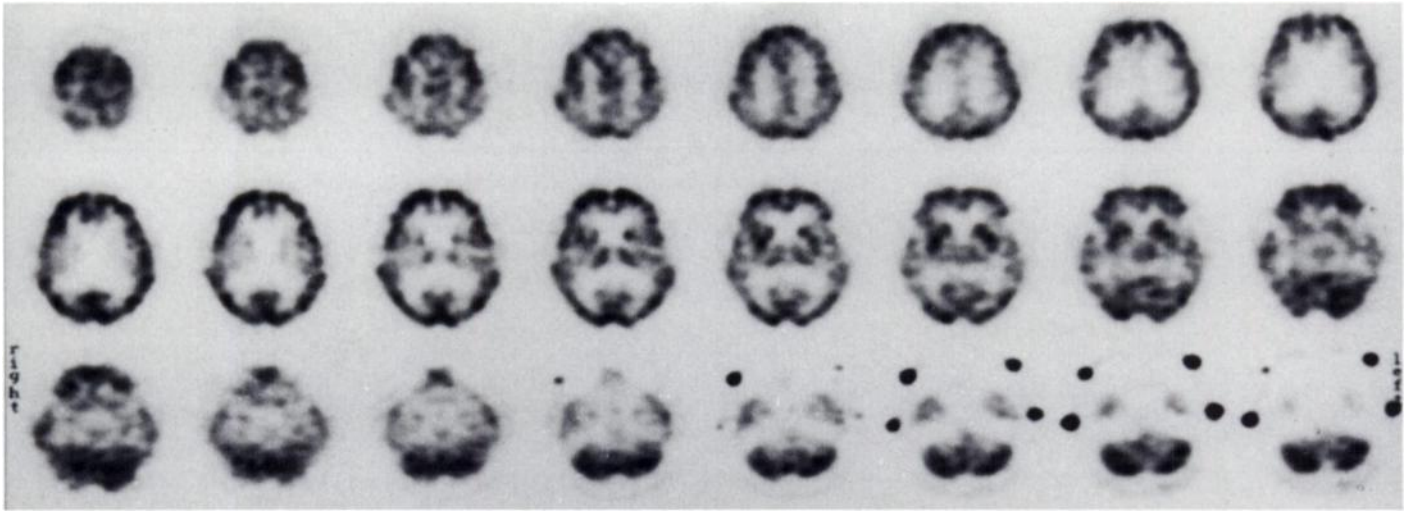

FIGURE 1. Oblique brain SPECT slices of a 78-yr-old woman (Patient 10) suffering from SDAT with a total hypoperfusion severity score of 5 and a bifrontal hypoperfusion severity score of 0. The SPECT images depict bitemporal hypoperfusion more at the left than right with slight involvement of both parietal lobes.

asymmetry. Figures 1 and 2 illustrate the perfusional differences between (S)DAT and FLD.

No significant correlation was found between MMSE score and total severity SPECT score. On the other hand, a weak though significant positive correlation was found between F_s scores and MFS scores in all patients. The MFS score was significantly higher in the FLD (5.4 ± 1.9; mean ± s.d.) than in the DAT group (2.1 ± 1.7; mean ± s.d.)($p < 0.001$). When temporal lobe hypoperfusion was examined uni- and bilaterally, no significant difference was found between FLD and (S)DAT. However, analysis of parietal and frontal lobe hypoperfusion yielded significant results. Biparietal hypoperfusion was found significantly more in (S)DAT ($p = 0.016$) and bifrontal hypoperfusion significanlty more in clinical FLD ($p = 0.0054$).

A logistic regression model predicting FLD versus (S)DAT based on SPECT results was developed. This step-wise test allowed significant discrimination between FLD and (S)DAT. The probablity of predicting (S)DAT based on the SPECT scan is calculated with the following formula:

$$p(DAT) = 1/[1 + e^{-(1.1 - 0.661 \times Fs)}],$$

where Fs is the severity score of bifrontal hypoperfusion. Using this equation, a value above 0.5 was predictive for (S)DAT and 74% of the SPECT studies of (S)DAT were correctly classified. A

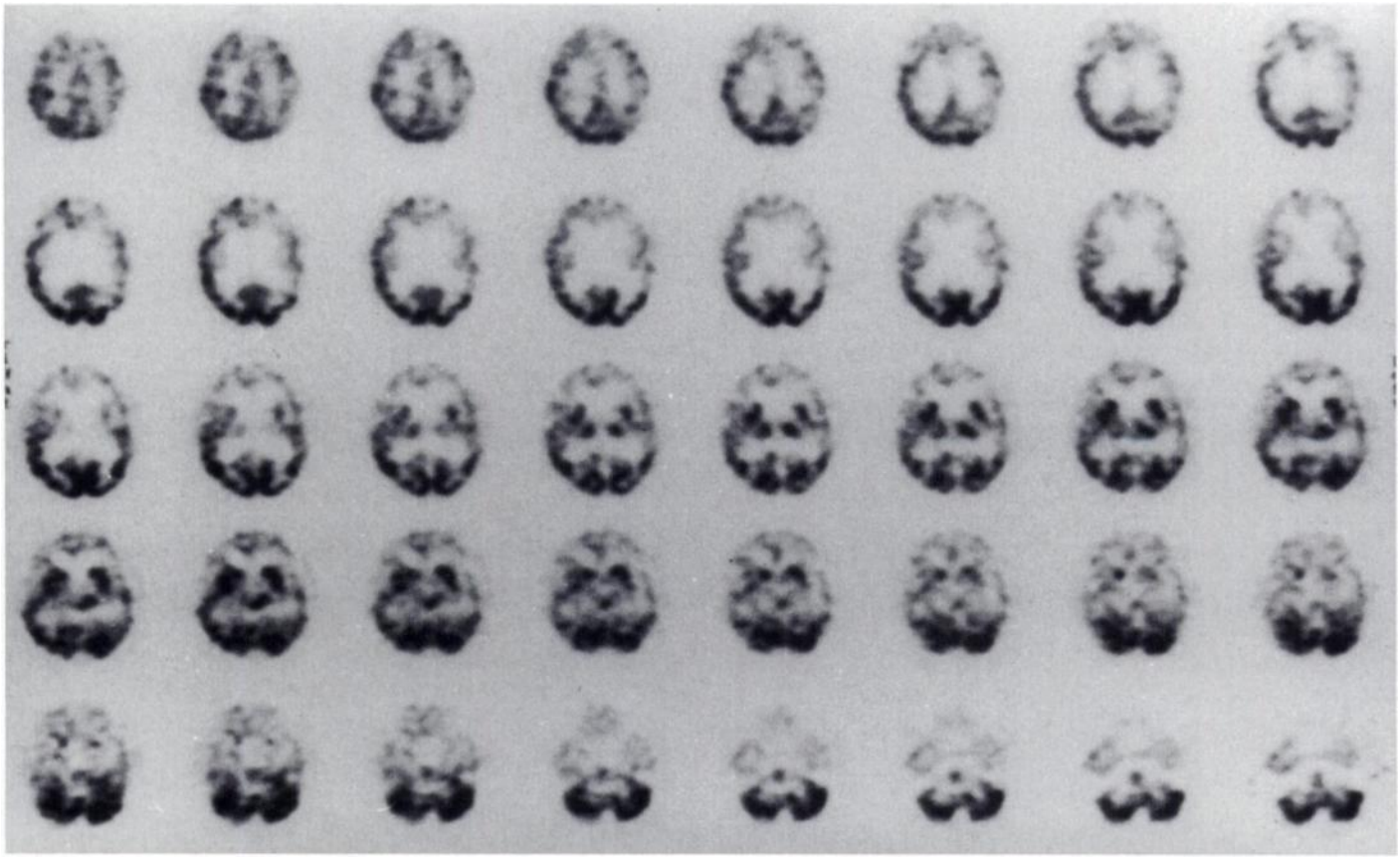

FIGURE 2. Oblique brain SPECT slices of a 46-yr-old man (Patient 33) suffering from FLD with a total hypoperfusion severity score of 7 and a bifrontal hypoperfusion severity score of 4. The SPECT images show marked bifrontal hypoperfusion, left temporal hypoperfusion and slight left parietal involvement.

calculated value below 0.5 was predictive for FLD and 81% of the SPECT studies of FLD were correctly classified.

Based on the Holman criteria, 34 of the 40 patients in our study were classified into categories C and D. There were 19 patients in category C, which amounted to 63% (S)DAT and 37% FLD. Category D included 15 patients of whom 27% had (S)DAT and 73% had FLD. Category E included two patients, both of whom had FLD.

DISCUSSION

MMSE scores do not correlate with severity on the SPECT scan in either group. The lack of correlation between MMSE scores and severity of SPECT deficit in our FLD group is consistent with the rCBF findings of Miller et al. (*9*) and is not surprising. Indeed, the MMSE test was only used as a tool for approximative severity matching of cognitive aspects in patient groups suffering from FLD and (S)DAT, which are qualitatively different clinical symptom complexes. In FLD, the first symptoms concern social conduct and are complicated only in later stages by cognitive decline. As a result, patients with initial FLD do not present to a memory clinic but to general practitioners or psychiatrists. In our study, mild FLD therefore is already complicated by cognitive decline. Due to the nature of the MMSE with overemphasis on temporal and spatial orientation, this cognitive involvement is not specific for frontal lobe decline. SDAT on the other hand is already initially characterized by cognitive decline and is only later characterized by conduct disorders such that MMSE-severity rating is more specific. To overcome this problem, however, new, short and comprehensive test batteries with multiaxial scoring will have to be developed. The actual MMSE results of our study therefore concern specific cognitive decline in (S)DAT and nonspecific extended cognitive symptomatology in FLD.

The lack of correlation between hypoperfusion severity and MMSE scores in our group of 19 (S)DAT patients is in contrast to the literature in which regional cerebral blood flow was found to correlate with severity of dementia (*22,23*). The population we studied was not stratified with respect to severity and MMSE scores as our aim was not to look for such a correlation, but rather at differential diagnosis. The MMSE may have more significance as a measure in combination with SPECT as a predictive or longitudinal tool when taking the temporal perfusion into account (*24*).

With respect to the perfusion pattern itself, significantly more frontal deficits were found in the patients with a clinical diagnosis of FLD and significantly more parietal deficits were found in patients diagnosed with (S)DAT. The correlation between parietal and or temporo-parietal hypoperfusion patterns and (S)DAT dates back to the late 1980s (*25,26*) and has been further validated in postmortem studies (*27*).

While early studies performed on patients with frontal type dementia used xenon, Neary et al. (*11*) described seven patients with dementia of the frontal type who underwent ^{99m}Tc-HMPAO SPECT imaging. These scans yielded higher resolution images. All of these patients exhibited selective reductions in tracer uptake in the anterior cerebral hemispheres, whereas patients with proven Alzheimer's disease showed reduced uptake in the posterior cerebral hemispheres. Miller et al. (*9*) reported on eight patients with FLD characteristics who had selective frontal hypoperfusion on their SPECT scans. The authors found SPECT to be extremely useful in delineating these patients from Alzheimer's disease patients.

Some findings indicate that patients clinically corresponding to FLD may not demonstrate the typical cerebral perfusion pattern previously described. Launes et al. (*28*) reported on a group of 160 patients wherein SPECT could differentiate only 2 of 5 clinically defined patients with FLD from other forms of dementia by SPECT.

Our logistic regression model, based on SPECT, allows discrimination between (S)DAT and FLD. The percentage that was well classified (81% of the FLD group and 74% of the (S)DAT group) might be an overestimation since it is based on the same data used to formulate the model. The model requires further validation with independent data to investigate whether it is still applicable to new groups of patients suffering from FLD and (S)DAT. To achieve this, we will calculate the percentage correctly classified in the new group, based on application of the old model. Nevertheless, the use of a logistic regression model for successful differential diagnosis between FLD and (S)DAT seems promising.

Using the Holman criteria, category E (frontal cortex defects only), we could select only 2 of the 21 (9.5%) patients with clinical FLD. However, by using the severity of bifrontal hypoperfusion, or the frontal severity score, rather than simply scoring presence or absence of hypoperfusion, we increased the diagnostic yield to 81%. The Holman criteria do not take into account severity of hypoperfusion and may not be applicable for a broad dementia population.

According to our results, SPECT is an important clinical tool in that it may give an additional biologic parameter. The tomographic information may further allow the clinician to estimate the extent and severity of disease as well as provide an important means for follow-up if quantified SPECT scanning could be performed. In helping to understand dementing illnesses, SPECT, compared to PET, is an affordable method for cummulative diagnostic yield. In the ongoing search for new treatment strategies in subpopulations of dementia, such as (S)DAT and FLD, which might respond differently to therapy, SPECT allows us to view functional repercussions to the brain. Moreover, early diagnosis is of particular importance in sociopsychological guidance and counseling given the different clinical presentation and prognosis of FLD and SDAT (*3*).

In conclusion, SPECT seems to be a potentially important functional neuroimaging tool for discrimination of FLD versus (S)DAT. Further validation of our logistic regression model is ongoing.

ACKNOWLEDGMENTS

This work was supported by the Flemish Ministry of Education, the Baron Bogaert-Scheid Fund, Born-Bunge Foundation, Medical Research Foundation OCMW Antwerp, University of Antwerp, the United Fund of Belgium and the NFWO grants 3.0044.92 and 3.0064.93.

REFERENCES

1. Gustafson L. Clinical picture of frontal lobe degenerations of the non-Alzheimer type. *Dementia* 1993;4:143–148.
2. Neary D. Dementia of frontal lobe type. *J Am Ger Soc* 1990;38:71–72.
3. Gustafson L. Frontal lobe degeneration of non-Alzheimer type. II. Clinical picture and differential diagnosis. *Arch Gerontol Geriatr* 1987;6:209–223.
4. Brun A. Frontal lobe degeneration of non-Alzheimer type. I. Neuropathology. *Arch Gerontol Geriatr* 1987;6:193–208.
5. Englund E, Brun A. Frontal lobe degeneration of non-Alzheimer type. IV. White matter changes. *Arch Gerontol Geriatr* 1987;6:235–244.
6. Risberg J. Frontal lobe degeneration of non-Alzheimer type. III Regional cerebral blood flow. *Arch Gerontol Geriatr* 1987;6:225–233.
7. Brun A. Dementia of frontal type. *Dementia* 1993;4:125.
8. Knopman DS. Overview of dementia lacking distinctive histology: pathological designation of a progressive dementia. *Dementia* 1993;4:132–136.
9. Miller BL, Cummings JL, Villanueva-Meyer J, et al. Frontal lobe degeneration: clinical, neuropsychologica, and SPECT characteristics. *Neurology* 1991;41:1347–1382.
10. Goulding P, Burjan A, Smith R, et al. Semi-automatic quantification of regional cerebral perfusion in primary degenerative dementia using technetium-99m-hexamethylproylene amine oxime and single photon emission tomography. *Eur J Nucl Med* 1990;17:77–82.

11. Neary D, Snowden JS, Northen B, Goulding P. Dementia of the frontal lobe type. *J Neurol Neurosurg Psych* 1988;51:353–361.
12. Ohnishi T, Hoshi H, Jinnouchi S, Nagamachi S, Wantanabe K, Mituyama Y. The utility of cerebral blood flow imaging in patients with unique syndrome of progressive dementia with motor neuron disease. *J Nucl Med* 1990;31:688–691.
13. Risberg J, Passant U, Warkentin S, Gustafson L. Regional blood flow in frontal lobe dementia of non-Alzheimer type. *Dementia* 1993;4:186–187.
14. Van Heertum RL. Clinical diagnosis: major depressive disorder. In: Van Heertum RL, Tikofsky RS, eds. *Cerebral SPECT imaging*, 2nd ed. New York: Raven Press; 1995:194.
15. Pohl P, Vogel G, Fill H, Rössler H, Zangerle R, Gerstenbrand F. Single-photon emission computed tomography in AIDS dementia complex. *J Nucl Med* 1988;29: 1382–1386.
16. Costa DC, Ell P, Burns A, Philpot M, Levy R. CBF tomograms with ^{99m}Tc-HMPAO in patients with dementia (Alzheimer type and HIV) and Parkinson's disease–initial results. *J Cereb Blood Flow Metab* 1988;8:S109–S115.
17. Neary D, Snowden JS, Mann DMA. The clinical pathological correlates of lobar atrophy. *Dementia* 1993;4:143–149.
18. Moretti JL, Sergent A, Louarn F et. al. Cortical perfusion assessment with ^{123}I-isopropyl amphetamine (^{123}I-AMP) in normal pressure hydrocephalus (NPH). *Eur J Nucl Med* 1988;14:73–79.
19. Cole MG, Dastoor D. A new hierarchic approach to the measurement of dementia. *Psychosomatics* 1987;28:298–305.
20. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurol* 1984;34:939–944.
21. Holman BL, Johnson KA, Greada B, Carvalho PA, Smith A. The Scintigraphic appearance of Alzheimer's disease: a prospective study using technetium-99m-HMPAO SPECT. *J Nucl Med* 1992;33:1941–185.
22. Johnson KA, Holman BL, Mueller SP, et al. Single-photon emission computed tomography in Alzheimer's disease. Abnormal I-123-iofetamine uptake reflects dementia severity. *Arch Neurol* 1988:45–392-396.
23. Eagger S, Syed GMS, Burns A, Barette JJ, Levy R. Morphologic (CT), and functional (rCBF SPECT) correlates in Alzheimer's disease. *Nucl Med Commun* 1992;13:644–647.
24. Wolfe N, Reed BR, Eberling JL, Jagust WJ. Temporal lobe perfusion on single-photon emission computed tomography predicts the rate of cognitive decline in Alzheimer's disease. *Arch Neurol* 1995;52:257–262.
25. Perani D, DiPiero 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.
26. McGeer PL, Kamo H, Harrop R, et. al Comparison of PET, MRI, and CT with pathology in a proven case of Alzheimer's disease. *Neurol* 1986;36:1569–1574.
27. Jobst KA, Smith AD, Barker CS, et al. Association of atrophy of the medial temporal lobe with reduced blood flow in the posterior parietotemporal cortex in patients with a clinical and pathological diagnosis of Alzheimer's disease. *J Neurol Neurosurg Psych* 1992;55:190–194.
28. Launes J, Sulkava R, Erkinjuntti T, et al. Technetium-99m-HMPAO SPECT in suspected dementia. *Nucl Med Commun* 1991;12:757–765.

Imaging Beta-Adrenoceptors in the Human Brain with (*S*)-1′-[^{18}F]Fluorocarazolol

Aren van Waarde, Ton J. Visser, Philip H. Elsinga, Bauke M. de Jong, Thom W. van der Mark, Jan Kraan, Kees Ensing, Jan Pruim, Antoon T.M. Willemsen, Otto-Erich Brodde, Gerben M. Visser, Anne M.J. Paans and Willem Vaalburg

PET Center, Department of Neurology and Department of Pulmonary Diseases, University Hospital and Department of Analytical Chemistry and Toxicology, University Center for Pharmacy, Groningen, The Netherlands; Institute of Pharmacology and Toxicology, Martin Luther University, Halle/Saale, Germany

We evaluated the suitability of fluorocarazolol for in vivo studies of cerebral beta-adrenoceptors because (*S*)-1′-[^{18}F]fluorocarazolol has a higher affinity to beta-adrenoceptors than to serotonergic receptors (pK_i β_1 9.4, β_2 10.0, 5HT_{1A} 7.4, 5HT_{1B} 8.1) and rapidly crosses the blood-brain barrier. **Methods:** The (*S*)-[^{18}F]fluorocarazolol (74 MBq, >37 TBq/mmol) was intravenously administered to healthy volunteers on two separate occasions with an interval of at least 1 wk. The initial injection was without pretreatment, but before the second injection, the volunteers received the beta blocker (±)-pindolol (3 × 5 mg orally, during 18 hr). The brain was studied with a PET camera in dynamic mode. **Results:** Uptake of radioactivity delineated gray matter and was particularly high in the posterior cingulate, precuneus and striatum. Low uptake occurred in the thalamus, whereas the lowest uptake was observed in the white matter of the corpus callosum. After pindolol pretreatment, uptake was reduced and its distribution became homogeneous throughout the brain. The ratio of total-to-nonspecific binding was about 2 at 60 min, increasing to 2.5–2.75 at longer intervals. **Conclusion:** Fluorocarazolol is the first radioligand that can visualize cerebral beta-adrenoceptors and may enable monitoring of these binding sites during disease.

Key Words: beta-adrenoceptors; brain; PET; fluorine-18-fluorocarazolol

J Nucl Med 1997; 38:934–939

An intriguing problem in biomedical research is that of relating symptoms of neurological as well as psychiatric disturbances to altered neurotransmitter binding in distinct regions of the brain. Cerebral beta-adrenergic binding sites for the neurotransmitter noradrenaline have been reported to be affected in a variety of disorders, such as depression (*1,2*), schizophrenia (*3*), alcoholism (*4*), Alzheimer's disease (*5*) and Huntington's chorea (*6*). They appear to play a role in many physiological and behavioral responses, such as glial proliferation (*7,8*), control of respiration (*9*), processing of visual information (*10*), memory function (*11*) and adaptation to stress (*12*). The generally observed delayed onset of action of antidepressant drugs may occur because downregulation of beta-adrenoceptors and serotonergic receptors takes place only after chronic drug administration (*13,14*). Receptor downregulation could be a prerequisite of the antidepressant activity (*15*). Receptor density may also change when noradrenergic innervation is impaired. Deterioration of noradrenergic neurons occurs such as in the Parkinson dementia complex (*16*).

Most of these observations have been made in autopsy studies, in binding assays to human lymphocytes and cultured cells or in animal experiments. None of these relationships has been observed in intact humans by external detection with receptor-specific radioligands. Fluorocarazolol, a fluorinated analog of the potent beta-blocker carazolol has been useful in in vivo studies of beta-adrenoceptors, both in experimental animals (*17–19*) and in humans (*20*). Uptake in the rat brain is saturable, sensitive to selective beta-adrenoceptor antagonists and stereospecific. We now report the first results obtained with (*S*)-1′-[^{18}F]fluorocarazolol-PET to visualize the distribution of beta-adrenoceptors in the brain of healthy volunteers.

Received May 31, 1996; revision accepted Oct. 23, 1996.

For correspondence or reprints contact: Dr. A. van Waarde, PET Center, Groningen University, Hospital, P.O.Box 30,001, 9700 RB Groningen, The Netherlands.