Comparison of CT, MR, and PET in Alzheimer's Dementia and Normal Aging

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We compared the findings of computed tomography (CT), magnetic resonance (MR), and positron emission tomography (PET) scans of glucose metabolism in 30 patients with clinically diagnosed Alzheimer's Disease (DAT) to those noted in 25 age-matched normal controls. Mean ratings of cortical and ventricular atrophy on CT and of metabolic abnormality on PET were significantly different ($p < 0.001$ and $p < 0.0001$, respectively) between two subject groups, however, there was a considerable overlap in reading of cortical atrophy. CT hypodensities were present in 17% of DAT patients and 12% of controls. MR revealed numerous additional periventricular and deep white matter signal changes. Neither hypodensities nor hyperintensities were correlated with PET abnormalities. Although, not infrequently, hypometabolic areas on PET scans corresponded to atrophic regions on anatomic images, they also occurred without such changes. Interestingly, cortical high signal intensity seen on MRI was frequently observed to be associated with areas of hypometabolism. Our results suggest that PET may be the most sensitive modality for detecting cortical involvement in DAT.

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The introduction of three powerful imaging modalities—x-ray computed tomography (CT), magnetic resonance imaging (MR), and positron emission tomography (PET)—has allowed detailed assessment of anatomic and functional abnormalities in various central nervous system (CNS) disorders. A large body of data emphasizes each technique's specific contribution to the detection and understanding of brain changes as a result of normal aging and dementing processes.

The important role of CT in the diagnostic evaluation of demented patients is undisputed (*1*). Besides allowing the exclusion of mass lesions or overt vascular damage to the brain, CT studies have also supported the notion of brain atrophy accompanying degenerative types of dementia (*2, 3*). Moreover, using sophisticated methods for calculating CSF containing spaces, a correlation between the degree of atrophy and psychometric parameters can be demonstrated in patients with dementia of the Alzheimer type (DAT) (*4, 5*). At this point in time, however, the information that may be extracted from CT scans has probably reached its limits.

In the last few years many studies in a variety of CNS disorders have demonstrated the high sensitivity of MR in detecting brain parenchymal abnormalities and have repeatedly stressed a superiority to CT (*6–9*). More recently a high incidence of white matter signal abnormalities on MR has also been documented in normal aging and DAT (*10–12*). The extent to which this information will have an impact on the evaluation of patients with DAT is still unclear.

The study of changes in brain metabolism by PET is yet another possible approach in enhancing our knowledge of normal brain aging and DAT. Given the coupling of brain function and metabolism, PET may prove to be a very sensitive test for detecting brain changes that accompany cognitive impairment. Widespread metabolic changes and a relatively characteristic pattern of abnormalities have been described in DAT (*13–17*).

Although clinical and histopathologic correlations will ultimately be needed to determine the significance

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of findings provided by CT, MR, and PET in DAT and normal aging, it seems appropriate to take the first step by comparing the in vivo results obtained with these modalities within the same group of subjects. We will therefore describe the type and frequency of brain abnormalities that have been detected with these techniques in a group of DAT subjects and in normal elderly controls.

STUDY POPULATION AND METHODS

Patient Selection and Clinical Assessment

All patients in this analysis were participants in an ongoing study of brain changes in normal aging and dementia at the University of Pennsylvania. The study protocol includes general physical and neurologic examinations and screening for the presence of cerebrovascular risk factors. Hachinski's Ischemia Score for dementia modified by Rosen (*18*), the Folstein-McHugh Mini-Mental State Examination (MMSE) (*19*), and the Blessed Dementia Scale (*20*) are routinely administered. In addition, all patients undergo extensive neuropsychologic testing and a laboratory workup consisting of electrolytes, complete blood count, vitamin B12 level, thyroid function testing, chest x-ray, EKG, and EEG. Brain imaging modalities consisted of CT, PET and, more recently, MR.

This report describes the data obtained from 30 subjects (mean age 65, age range 52 to 80 yr) with the clinical diagnosis of Alzheimer's disease (DAT) and from 25 age-matched controls (mean age 65 yr, age range 46 to 83 yr). Demented subjects included in this study were screened using the diagnostic criteria of the DSM III (*21*) and of the NINCDS-ADRDA Work Group on Alzheimer's disease (*22*). Applying the latter criteria 24 patients were categorized as probable and 6 as possible cases of DAT. DAT patients also had to score <2 on Rosen's modification of Hachinski's Ischemia Score (*18*). Developed on the basis of autopsy findings this score appears to be reliable in detecting cases of vascular dementia. The severity of dementia as assessed by the 30-point MMSE ranged from 29 to 4. The degree of dementia was mild to moderate (MMSE scores >15) in 14 patients, moderate to severe (MMSE scores <15) in 16 DAT subjects. Controls were elderly individuals without clinical evidence of dementia or any other psychiatric illness. They were recruited from retirement communities and 12 were spouses of demented subjects. Minor noncardiovascular disease (e.g., treated thyroid disease, minor gastrointestinal complaints) was present in six individuals, mild cardiovascular disease (treated hypertension) was found in 11 controls (*23*). These findings were comparable to the medical state of the DAT group. DAT and control individuals were asked to discontinue (if medically feasible) any medication 1 wk prior to the initiation of the study.

Imaging Modalities

Computed tomography. Twenty-eight of thirty DAT patients and 25 control subjects underwent CT using GE 8800 or GE 9800 CT scanners. Slices were obtained with a thickness of 5mm in the majority of patients and no contrast material was used.

Magnetic resonance. Magnetic resonance imaging (23 DAT patients, 10 controls) was performed using a GE 1.5 Tesla superconducting magnet and a multislice spin-echo technique. The present analysis was performed on axial images only. These were generated with a pulse repetition time of 1500 to 2500 msec and two echos (T_E 25–120 msec) yielding mixed intensity and T2-weighting. The slice thickness of MR scans varied from 5–8mm.

Positron emission tomography. Positron emission tomography was carried out in 30 DAT and 25 control subjects. Local cerebral glucose metabolism was determined using the fluorine-18 fluorodeoxyglucose ([^{18}F]FDG) technique. Details of this method have been described elsewhere (*24*). The scanner used is a modified version of the PETT V system (*25*). It simultaneously generates seven cross-sectional images of the brain along the rostrocaudal axis. Two sets of scans, routinely obtained in every patient, yield a total of 14 overlapping image slices per session. Scanning time is adjusted so that a minimum of 1 million counts per slice is obtained.

Scan Interpretation

For each imaging modality the scans obtained from DAT and control subjects were randomly mixed and interpreted separately by a neuroradiologist (CT and MR) and a nuclear medicine specialist (PET). No information as to age, sex, or clinical condition of the patient was available to the readers. The extent of cortical and ventricular atrophy on CT and MR and the severity of metabolic abnormalities present on PET were rated on a 4 grade scale (absent, mild, moderate, severe). The presence of focal abnormalities (e.g., circumscribed areas of atrophy, areas of hypodensity on CT, abnormal high signal on MR or hypometabolism on PET) was documented on templates corresponding to each transverse image. An anterior to posterior gradient of cortical atrophy or lateral asymmetry were also indicated.

Analysis

The type, frequency and extent of abnormalities detected by CT, MR and PET were listed for DAT and control subjects. The Mann-Whitney U (*26*) test corrected for tied ranks was used to compare the mean rank of ratings of cortical and ventricular atrophy and the degree of metabolic abnormality between two groups. Differences in ratings of hypometabolism, cortical atrophy, and ventricular atrophy between DAT patients with a MMSE >15 and those below were tested using the Kolmogorov–Smirnov two sample test (*27*) to determine whether two independent samples were drawn from the same population. The correlation of anatomic and metabolic findings was assessed by visually comparing the location and extent of CT, MR, and PET abnormalities as documented on the templates during blind reading. Because of the different number of subjects studied with each modality, comparisons were made separately among those having had CT and PET scans and the group of subjects studied by all three imaging techniques.

RESULTS

Computed Tomography

Higher grades of cortical and ventricular atrophy were more often found in DAT patients than in age-matched normal controls and the differences in the

TABLE 1
Comparison of CT Evidence of Cortical Atrophy, Ventricular Atrophy, and Brain Metabolic Abnormality as Discriminators Between Normal Aging and DAT

	Controls (25)	DAT (28)	Level of significance*
Mean ranks of ratings:			
Cortical atrophy (CA)	0.92 ± 0.70	1.79 ± 0.96	$p < 0.001$
Ventricular atrophy (VA)	0.36 ± 0.64	1.54 ± 1.04	$p < 0.001$
Brain hypometabolism (HM)	0.24 ± 0.60	2.00 ± 0.86	$p < 0.0001$
Mean differences in ratings:			
CA-VA	0.56 ± 0.71	0.25 ± 1.04	N.S.
CA-HM	0.76 ± 0.78	−0.22 ± 1.06	$p < 0.005$
VA-HM	0.20 ± 0.64	−0.47 ± 0.96	$p < 0.01$

* Mann-Whitney U test.

mean rank of rating scores of both features between these groups were highly significant (Table 1). Nevertheless, there was a considerable overlap in atrophy scores between both groups (Table 2). Ventricular atrophy was ranked significantly higher in DAT patients with a MMSE <15 than in those patients with milder degrees of dementia. A significant difference was not observed, however, for the rankings of cortical atrophy (Table 1). Areas of hypodensity in the white matter adjacent to the lateral ventricles were present in three controls (12%) and five DAT (17%) patients. In one of these control subjects an additional ill-defined area of hypodensity separated from the periventricular abnormality was noted in the deep white matter. A small infarct involving the cortical gray matter was seen in one DAT patient. The distribution of these abnormalities with respect to the severity of the dementing illness is seen on Tables 2 and 3.

Magnetic Resonance

As with CT there was more extensive cortical and ventricular atrophy noted on MR scans of DAT patients than of controls (Tables 1 and 2). Periventricular and/or deep white matter signal abnormalities were seen in 6/10 (60%) controls and 10/12 (83%) DAT patients. Areas of cortical high signal intensity were noted in 6

TABLE 2
Anatomic Abnormalities in Normal Aging and DAT as Detected by CT and MR

	CT			MR	
Abnormality (score)	Controls (25)	DAT (28)	(>15, <15)* (14, 14)	Controls (10)	DAT (12)
Cortical atrophy					
None (0)	7	4	(3, 1)	1	1
Mild (1)	13	4	(3, 1)	5	2
Moderate (2)	5	14	(7, 7)	4	6
Severe (3)	0	6	(1, 5)	0	3
Ventricular atrophy					
None (0)	18	6	(5, *1)	6	1
Mild (1)	5	6	(5, 1)	3	3
Moderate (2)	2	11	(4, 7)	1	7
Severe (3)	0	5	(0, 5)	0	1
White matter lesions†					
Periventricular	3	5	(2, 3)	5	10
Deep White Matter	1	0	(0, 0)	6	8
Gray matter lesions†					
Cortical	0	1	(0, 1)	0	6
Subcortical	0	0	(0, 0)	1	3

* DAT patients with Mini Mental State Exam >15 or <15 (30 = normal score).

† Lesion refers to areas of hypodensity on CT and of high signal intensity on MR scans obtained with imaging parameters described in text.

* Kolmogorov-Smirnov Two Sample Test: $K_D > 8$ (one-tailed, $p = 0.01$), the ratings of ventricular atrophy are significantly more extensive for DAT patients with MMSE score <15 and >15.

TABLE 3
Comparison of Anatomic Findings by CT and MR Versus Glucose Metabolism by PET

Control (Age)	MR				PET
	CT areas of hypodensity*†	White matter lesions*†	Gray matter lesions‡	MR/CT regional atrophy	cortical hypometabolism
1–61	—	—	—	A > P	—
2–64			—	—	—
3–76	—	—	—	P > A	—
4–70	—	Caps Rf + Lo, 30–50 PF fpo bilat.	—	P > A	—
5–52	—	1PF Ro	—	P > A	—
6–76	—	Thin lining, 10–30 ECF fp bilat.	—	Lo	—
7–65	—	—	—	P > A, R > L	Mild f bilat.
8–72	—	Thin lining 10–30 PF p bilat.	PF in BG bilat.	L > R	Mild f + p bilat.
9–68	Caps o bilat. 1 lesion Rp	Lining, 10–30 ECF po bilat.	—	R insula	Mild f bilat.
10–83	Caps o bilat.	Lining, caps 0 10–30 ECF po bilat.	—	P > A	Moderate f bilat.
DAT(MMSE)§					
11–52 (28)	—	—	—	—	Mild f bilat.
12–66 (29)	—	—	—	P > A	Mild Lf+ Moderate Lp
13–70 (23)	—	"Halo"	Insular CH bilat.	Lfp	Moderate Lft
14–77 (20)	—	"Halo", 30–50 PF po bilat.	Insula + uncohippo campal CH L > R, BG	R Insula	Mild global, moderate f bilat.
DAT age (MMSE)§					
15–66 (19)	—	"Halo"	—	P > A	Mild f, moderate p Bilat.
16–71 (17)	Caps Lf + Lo	"Halo", 30–50 PF +ECF fp bilat	Insula + uncohippocampal, CH L > R, BG	P > A, L > R	Moderate p L > R + t bilat.
17–80 (17)	—	"Lining" 30–50 PF f > p bilat.	BG	Pp L > R	Mild global Moderate f bilat.
18–57 (15)	NA	"Lining" <10 PF Rf	Insula+ uncohippocampal CH L > R, Rt	L > R, Rt	Moderate global, severe Lfr + t bilat.
19–67 (13)	"lining" caps f+o bilat	"Halo", 10–20 ECF fpo R	L insula + uncal CH bilat., BG	p bilat.	severe fpt bilat. R > L
20–61 (10)	—	"Lining", 10–20 PF bilat.	—	L P. horn	Moderate Lf+ severe pt L > R
21–62 (8)	NA	"Halo", >50 ECF fp bilat.	Insula + uncohippocampal CH L > R	tL > R	Moderate global severe L fpt
22–68 (4)	—	"Lining", <10 ECF fp bilat.	—	Lt T/tip, L lateral ventricle	Severe global, severe Lfpt + Rpt

* L = Left, R = Right, A = Anterior, P = Posterior, f = Frontal, p = Parietal, O = Occipital, t = Temporal, NA = Not Available.
† "lining" = thin rim of hypodensity (CT) or hyperintensity (MR) around lateral ventricles, "halo" = smooth band of hypodensity (CT) or hyperintensity (MR) around lateral ventricles, PF = punctate foci of hyperintensity, ECF = early confluent foci of hyperintensity.
‡ C = cortical high signal intensity, BG = punctate hyperintense foci in basal ganglia.
§ MMSE = Mini Mental State Examination.

patients with DAT only. Tables 2 and 3 provide a detailed description of these findings. The pattern of signal abnormalities seen in normal aging and Alzheimer's disease has been reported elsewhere (*12*).

Positron Emission Tomography

Based on visual interpretation and thus relative metabolic activity, PET scans were ranked as normal in 21 of 25 aging controls. Mild metabolic abnormalities were

TABLE 4
Metabolic Abnormalities in Normal Aging and DAT as Detected by PET

	Controls (25)	DAT (28)	(>15, <15)* (14, 14)
Severity of hypometabolism			
None	21	1	(0, 1†)
Mild	3	7	(5, 2)
Moderate	1	12	(8, 4)
Severe	0	8	(0, 8)

* DAT patients with Mini Mental State Exam >15 and <15.
† Kolmogorov-Smirnov Two Sample Test: $K_D > 8$ (one tailed, $p = 0.01$), the ratings of metabolic abnormality are significantly more severe for DAT patients with MMSE score <15 and >15.

present in three, and a moderate abnormality in one control subject. In contrast, only one PET scan of 30 DAT patients was read as normal (Table 4). The rank scores of hypometabolism in DAT patients were significantly higher when compared to those obtained in controls (Table 1). The ratings of hypometabolism are significantly more severe with increasing cognitive impairment (MMSE <15 versus MMSE >15—Table 4) and global cortical involvement was predominantly seen in patients with severe dementia (Table 3).

Comparison of CT and PET

The mean rank of ratings of cortical atrophy, ventricular atrophy and brain metabolic abnormality were all significantly different between normally aged subjects and DAT patients, but both groups were separated best on the basis of metabolic assessment. On CT a mild anterior-posterior gradient and/or lateral asymmetry of cortical atrophy was present in 13 of 25 controls. More focal atrophic changes were seen in another four normal individuals. The areas of frontal hypometabolism noted on PET scans of four controls did not correspond to frontal atrophic changes (see Patients 7, 8, 9, 10, Table 3, and Figure 1). Focal atrophy ranging from mild to severe was seen in 15 of 28 DAT patients with more diffuse lateralized or anterior-posterior differences in another 11. The pattern of metabolism as displayed by PET matched the distribution of atrophy in nine cases. In the remaining 19 DAT patients PET abnormalities were present without corresponding regional atrophic changes (Fig. 2). Severe focal atrophy was most likely to be associated with apparent local hypometabolism, whereas the presence of atrophy could not be predicted on the basis of a hypometabolic lesion (Fig. 3).

Comparison of CT, MR, and PET

Cortical atrophy was rated alike in 18 of 20 DAT patients and controls studied by CT and MR. Ventricular changes were assigned the same rank in 14 instances. In the remainder cortical and ventricular changes were ranked with the same frequency of less or more atrophy (enlargement) and ratings did not differ more than one rank. The areas of hypodensity visualized on the CT scans of controls 9, 10 and DAT Patients 14, 16, 18 were all delineated as regions of abnormal high signal intensity on MR. MR demonstrated additional periventricular hyperintense lesions (see MR results and Tables 2, 3) in another three controls and four DAT subjects. Focal MR signal abnormalities in the deep white matter were not associated with corresponding CT lesions except for one ill-defined area of hypodensity in the parietal white matter of control Patient 9, Figure 1. There was no obvious relationship between areas of cortical hypometabolism as seen on PET and

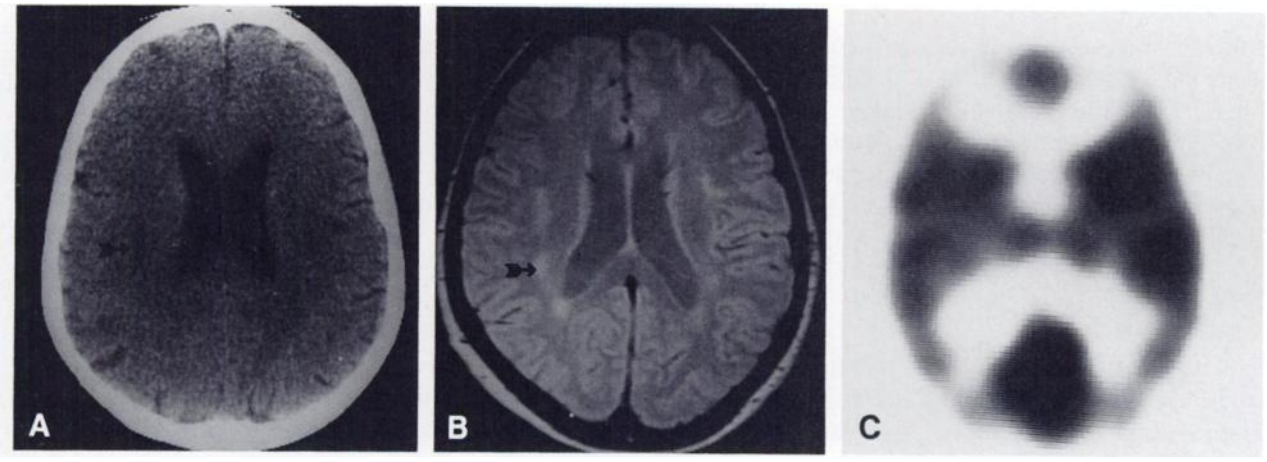

FIGURE 1
Normal elderly subject (Patient 9). A: CT shows cortical and ventricular atrophy. An ill-defined area of hypodensity is noted in the right parietal deep white matter (arrow). B: MR demonstrates a thin line of high signal intensity around the lateral ventricles. Numerous early confluent foci of high signal intensity (one focus corresponding to the hypodensity seen on CT-arrow) are present in the deep white matter bilaterally. C: PET reveals a mild reduction of glucose metabolism bifrontally.

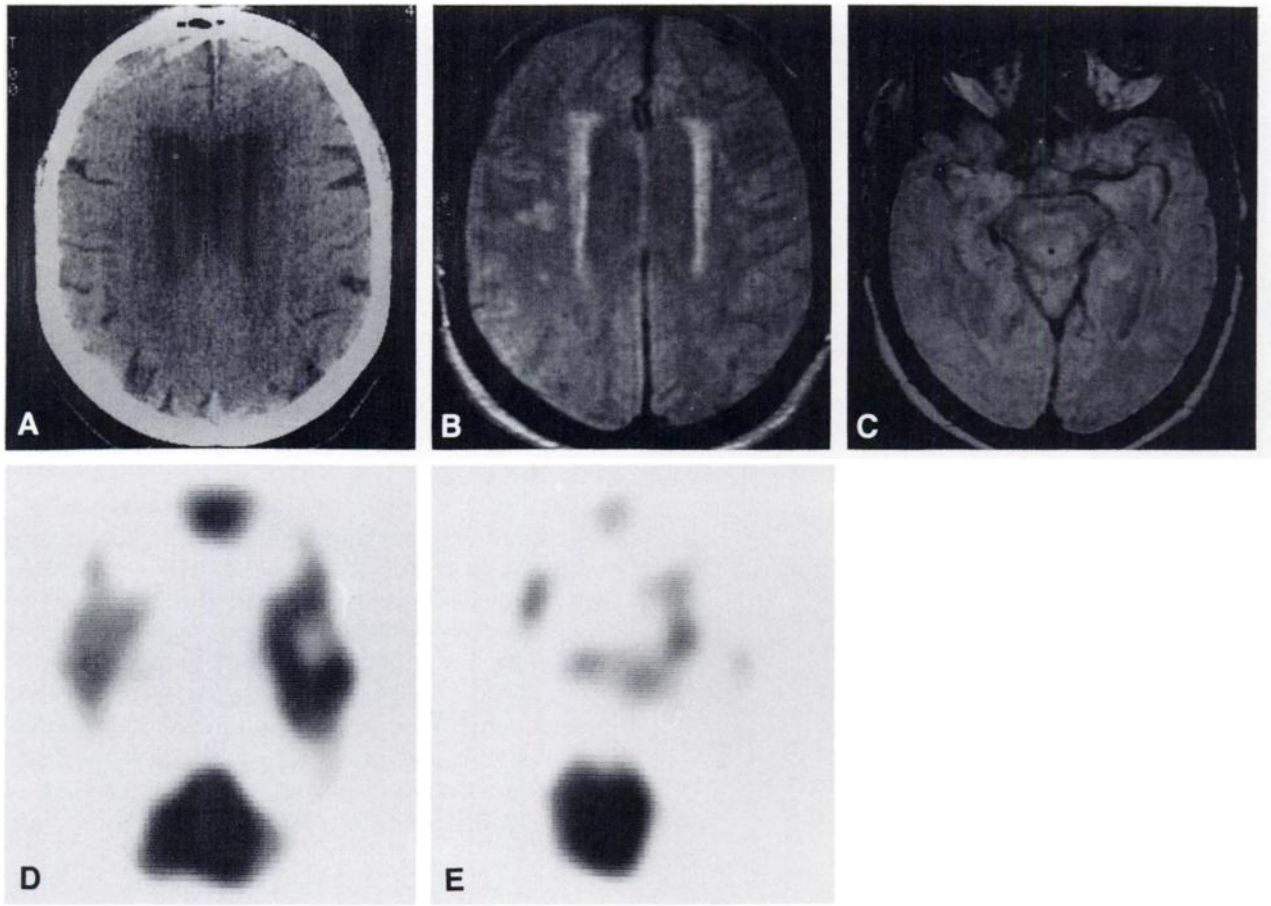

FIGURE 2
Patient with DAT (Patient 19). A: CT shows moderate cortical and mild ventricular atrophy. A band of hypodensity surrounds the lateral ventricles (most prominent anteriorly and posteriorly). B: MR at the same level demonstrates a "halo" of periventricular high signal intensity. Ten to twenty early confluent foci of hyperintensity are noted in deep white matter predominantly on the right. C: MR section through the temporal lobes reveals bilateral uncal hyperintensity. D: PET at a level corresponding to A and B reveals a global reduction of glucose metabolism, more so on the right. The sensorimotor cortex appears to be relatively spared. E: The temporal lobes are severely hypometabolic. Preserved metabolism is noted in the occipital cortex.

either CT hypodensities or periventricular and/or deep white matter MR lesions (Table 3). Cortical high signal intensity (e.g., insular and unco-hippocampal) on MR (Patients 13, 14, 16, 18, 20, 22) however, was frequently seen within larger areas of hypometabolism on PET scans (Figure 2).

DISCUSSION

In view of the large number of reports describing separately the specific features of either CT, PET and more recently MR in normal aging and Alzheimer's disease we will predominantly focus on comparing the different findings provided by these imaging techniques obtained in the same subjects. To our knowledge this is the first time that such a comparison has been carried out in a large group of subjects.

CT results on cortical and ventricular atrophy in this study are in agreement with previous reports showing that a significantly higher degree of sulcal and ventricular CSF space enlargement is observed with DAT (*2, 3*). The extent of atrophy increases with the severity of the dementing illness. Individuals can, however, not be classified as normal or demented based on visual assessment of atrophy partly because of a considerable overlap in its extent between both groups. A clearer distinction may be expected by applying quantitative measures of atrophy (*2,28*) and MR may facilitate and improve CSF space determination (*28,29*).

In our study, control subjects and demented patients could be clearly separated on the basis of metabolic findings. Whereas only four of 25 controls showed mild to moderate cortical hypometabolism, all but one demented patient had signs of cerebral metabolic impairment. These abnormalities were predominantly focal in the early stages of DAT, while diffuse metabolic depression was noted in more advanced cases.

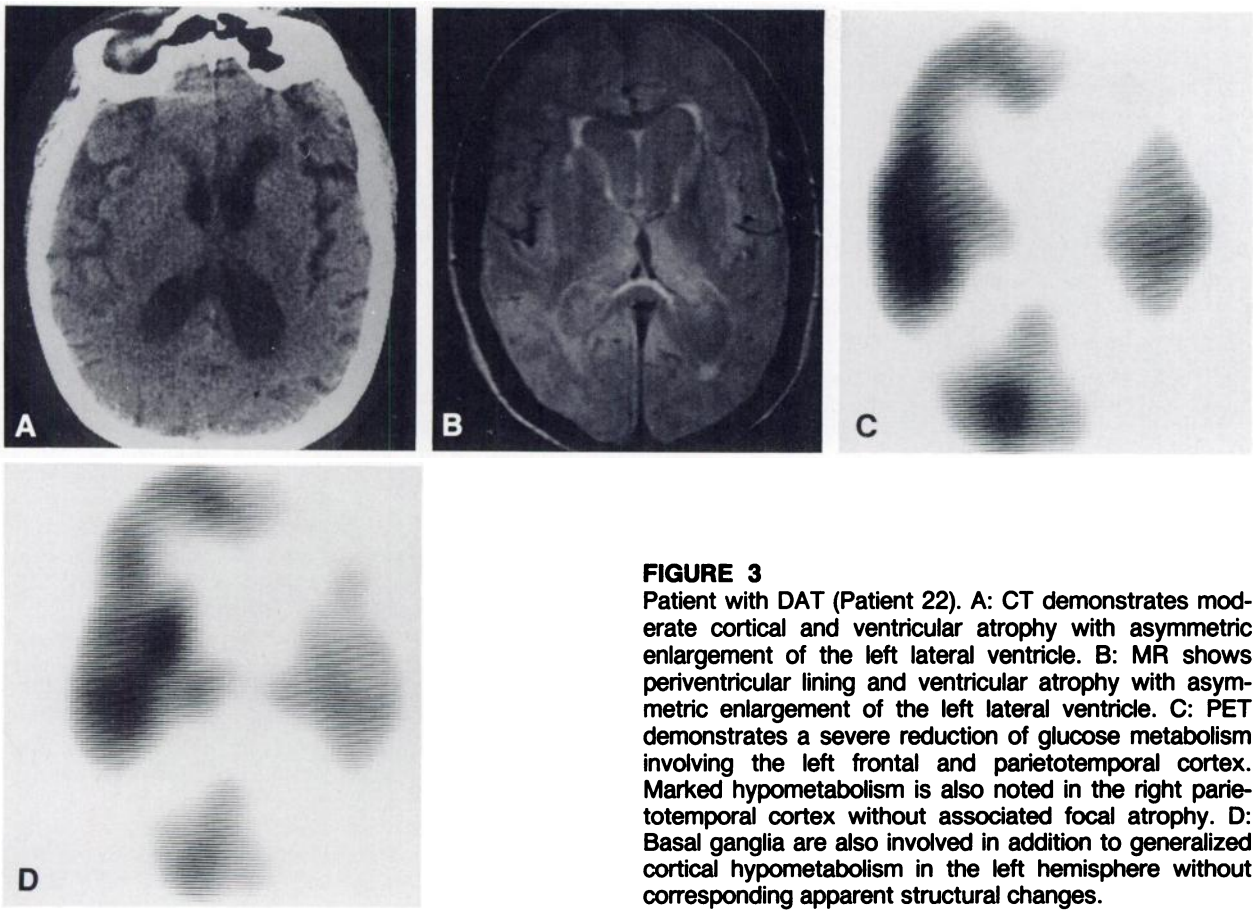

FIGURE 3
Patient with DAT (Patient 22). A: CT demonstrates moderate cortical and ventricular atrophy with asymmetric enlargement of the left lateral ventricle. B: MR shows periventricular lining and ventricular atrophy with asymmetric enlargement of the left lateral ventricle. C: PET demonstrates a severe reduction of glucose metabolism involving the left frontal and parietotemporal cortex. Marked hypometabolism is also noted in the right parietotemporal cortex without associated focal atrophy. D: Basal ganglia are also involved in addition to generalized cortical hypometabolism in the left hemisphere without corresponding apparent structural changes.

MR has called attention to the presence of white matter signal abnormalities in normal aging and demented subjects (*10–12*). The frequency of white matter hypodensities reported in recent CT studies (*28–30*) for patients with DAT and elderly normals has increased compared to previous observations (*31,32*). This may be explained by an improvement in scanner contrast resolution. A higher rate of awareness of such lesions stimulated by MR findings may also be a contributing factor. Despite specific attention given to periventricular and white matter lesions on CT, our study did not reveal as high an incidence of hypodensities in DAT patients as reported by others recently (*30,31*). There was also no significant difference to the frequency with which such abnormalities were seen in age-matched controls compared with DAT patients.

White matter lesions were visualized much more frequently by MR than by CT. Punctate and even early confluent MR foci of high signal intensity most often had no CT correlates. In patients with periventricular CT hypodensities the abnormality appeared to be larger and better defined on MR.

Metabolic abnormalities present on PET scans could neither be related to the location of the deep white matter or periventricular signal abnormalities present on MR scans nor to the hypodensities seen on CT. Histopathologic data (*32, 33*) and a concomitant reduction of white matter flow (*34*) suggest a vascular origin to MR white matter lesions. Interestingly enough, no metabolic depression of overlying cortical areas was observed either in controls or in mild to moderately demented patients. The visual interpretation of metabolic changes in the white matter itself is hampered by its relatively low metabolism compared to cortex. White matter signal abnormalities also did not explain the extensive hypometabolism in severely affected DAT patients. In such cases MR white matter lesions appeared to be located adjacent to the areas of metabolic abnormality by chance alone. Widespread metabolic impairment in many DAT patients may also explain the frequent presence of focal cortical high signal lesions on MR in areas of hypometabolism on PET. It is of interest that these cortical hyperintensity abnormalities were seen in DAT patients only.

Focal metabolic abnormalities were only in part associated with regional cortical atrophic changes. Studies of our group and of other investigators have called attention to the extent to which brain atrophy may influence calculations of absolute metabolic rates. The effect of correction for atrophy on global as well as regional metabolic values has been reported (*28,35,36*). Comparing the patterns of metabolic impairment and

atrophic changes in this series has demonstrated, however, that by visual criteria the majority of focal metabolic abnormalities cannot be explained on the basis of cortical atrophy alone. In a comparative case study including pathology, regional hypometabolism could also not be accounted for by the presence of cortical atrophy but matched the pattern of histopathologic changes typical for Alzheimer's disease (*37*). These results confirm that metabolic dysfunction may be the first indication of a degenerative cortical process in DAT, whereas anatomic changes like cortical atrophy, while still associated with hypometabolism, become evident on CT or MR only later in the course of the disease process.

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