Differential Diagnosis of Alzheimer's Disease with PET

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PET studies have demonstrated bilateral temporo-parietal hypoperfusion and hypometabolism in probable and definite Alzheimer's disease (AD), a pattern that may help differentiate AD from other dementias. **Methods:** To evaluate the diagnostic power of cerebral metabolic distribution patterns for "cortical" degenerative dementias, PET scans obtained from 129 patients referred for differential diagnosis of dementia were analyzed visually. **Results:** Sixty-five patients had a final clinical diagnosis of probable AD. Ninety-seven percent (97%) of those had abnormal metabolic scans and 94% showed a suggestive pattern of bilateral or unilateral temporo-parietal hypometabolism (with or without frontal involvement). Hypometabolism was unilateral in 23% of patients. Five subjects with a neuropathologically proven diagnosis of Alzheimer's disease had a suggestive metabolic pattern. One of those was an early case with frontal hypometabolism exceeding temporo-parietal involvement. Two patients with Alzheimer's-type dementia had isolated bilateral frontal hypometabolism. **Conclusions:** This alternative metabolic pattern may correspond to a nonAlzheimer pathology occurring in 10%–20% of patients suffering from clinically probable Alzheimer's disease. Most of the patients with possible but atypical Alzheimer's-type dementia showed isolated bilateral frontal involvement. This metabolic pattern probably corresponds to different diseases, such as Pick's disease, frontal lobe dementia or progressive subcortical gliosis.

Key Words: dementia; Alzheimer's disease; positron emission tomography

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PET studies have demonstrated characteristic bilateral temporo-parietal hypoperfusion and hypometabolism in probable (*1*) and definite (*2*) Alzheimer's disease (AD). This pattern might help to differentiate AD from frontal lobe dementia (*3*), primary progressive aphasia without dementia (*4*), normal pressure hydrocephalus (*5*) and multi-infarct dementia (*6*).

Predominant unilateral hypometabolism, however, may occur in early AD (*7*). Frontal involvement may eventually appear during the disease (*1*), and bilateral temporal and parietal blood flow or metabolic impairment have been described in Parkinson's disease and dementia (*8*), vascular dementia (*1,9*) and Creutzfeldt-Jakob disease (*10*).

A recent SPECT study emphasized the scintigraphic appearance of AD (*11*). We performed a similar study to evaluate the role of visual analysis of PET metabolic patterns for the differential diagnosis of degenerative dementias.

METHODS

Subjects

We analyzed PET studies obtained from 129 patients referred for differential diagnosis of dementia. The mean age was 64.8 ± 10.5 yr. Severity of dementia was rated as 1 (mild), 2 (moderate) or 3 (severe) according to the Clinical Dementia Rating (*12*). Clinical history, neuropsychological examination, complementary investigations and follow-up helped to establish the final diagnosis (see Table 1) with sufficient confidence.

Probable AD (n = 65) was diagnosed in accordance with NINDS/ADRDA criteria (*13*) after careful medical, neurological and psychiatric examination, laboratory tests, EEG and CT. Eight of these patients initially had isolated cognitive or psychiatric symptoms before clinical evolution showed that they suffered from probable AD (which was their final diagnosis): three patients presented with slowly progressive aphasia, three others with depression and two with predominant memory impairment. Five patients received a definite diagnosis of AD after neuropathological examination. Probable and definite AD cases were mostly presenile, having a mean age of 65.9 ± 7.4 yr and a mean disease duration of 2.5 ± 1.9 yr at the time of PET evaluation. Mean severity of dementia was rated as 2.1 ± 0.8 (*12*).

Other patients (n = 19) fulfilled the criteria for possible AD (*13*), but their degenerative dementia (*14*) was atypical, e.g., predominant behavioral changes or early loss of insight, and relative preservation of memory, spatial orientation or visuospatial functions (DEM). It was not always possible to administer "formal" frontal tests such as the Wisconsin Card Sorting test or the Stroop test to patients due to severity of the dementia, personality disturbances or aphasia. The population was heterogeneous, and seven patients initially had isolated cognitive or psychiatric symptoms before clinical evolution showed that they were demented: three patients suffered from slowly progressive aphasia with subsequent dementia and four had behavioral disturbances first con-

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sidered to be psychiatric, but later diagnosed as a frontal type dementia. Two patients with DEM received a definite diagnosis of Pick's disease. Another had a neuropathologically proven diagnosis of progressive subcortical gliosis (*15*). The mean age in this group was 59.5 ± 10.6 yr, and mean disease duration was 2.6 ± 1.8 yr (at the time of PET). Mean severity was rated as 2.0 ± 0.8.

Parkinsonian patients (n = 13) were referred when dementia occurred. They were 72.6 ± 4.1 yr old; the dementia duration was 3.0 ± 2.7 yr and the severity of dementia was scored as 2.5 ± 0.5. One patient with parkinsonism suffered from progressive supranuclear palsy (PSP) (*16*).

Patients with vascular dementia (n = 8) had a Hachinski score (*17*) above 5 and an abnormal CT scan. They were 62.2 ± 6.0 yr old, dementia duration was 2.9 ± 2.7 yr and severity was scored as 1.9 ± 0.6. The diagnosis of vascular dementia was probable or possible according to criteria proposed by Chui et al. (*18*). However, when the clinical scenario was compatible with both possible AD and possible vascular dementia (a single stroke and vascular risk factors), dementia was considered to be mixed (n = 9). These patients were 68.8 ± 6.9 yr old, the dementia duration was 3.6 ± 1.8 yr and dementia severity was 1.9 ± 1.0.

Creutzfeldt-Jakob disease (n = 3) and adult metachromatic leucodystrophy (n = 1) were determined after postmortem neuropathological confirmation. One patient became demented after cerebral anoxia. Primary progressive aphasia (PPA, n = 2) consisted of long duration speech difficulties without dementia (*4*). Cerebral ventricular pressure monitoring and evaluation after ventriculo-peritoneal shunting confirmed the diagnosis of normal pressure hydrocephalus (n = 3). Patients with depression (n = 4) progressively improved under appropriate medication.

Imaging

PET scans were acquired in the resting state, with eyes closed and minimal ambient noise on a NeuroEcat (EG&G ORTEC, medium resolution) with axial and transverse resolution of 15.0 and 12.4 mm FWHM respectively. Data reconstruction and analysis have been presented elsewhere (*19,20*). Briefly, after an 8-mCi bolus intravenous injection of ^{18}F-fluorodeoxyglucose, arterial blood samples were obtained for an input function. Images were acquired 40 min after tracer injection. Each acquisition consisted of two transverse planes parallel to the orbito-meatal line (32-mm interval), and successive displacements of the tomograph table enabled studies at 10–12 different levels. Attenuation correction was performed with a skull fitting, operator-drawn ellipse. The operational equation derived by Phelps et al. (*21*) was used to obtain transverse images of the regional distribution of cerebral metabolic rates of glucose (mg · 100 g · min^{-1}). Region of interest and visual analyses were performed on seven parallel planes (*19,20*) selected according to the Eckernas and Aquilonius brain atlas (*22*). They ranged from 2.2 to 7.0 cm above the orbito-meatal line of reference (8-mm interval). Calculated metabolic images were preferred to scintigraphic pictures because they provided better interregional contrast.

PET images were classified according to several patterns (Fig. 1):

1. Bilateral temporo-parietal hypometabolism (with or without frontal involvement).
2. Unilateral temporo-parietal (with or without frontal) involvement.
3. Frontal metabolism bilaterally more affected than the temporo-parietal one.
4. Frontal metabolism unilaterally more affected than the temporo-parietal one.
5. Isolated bilateral frontal involvement, sometimes asymmetrical.
6. Left perisylvian decrease of metabolism, sometimes extending to homolateral cortices.
7. Diffuse cortical hypometabolism localized above the level of the basal ganglia.
8. Multiple, patchy foci of cortical and subcortical hypometabolism.
9. Normal distribution.

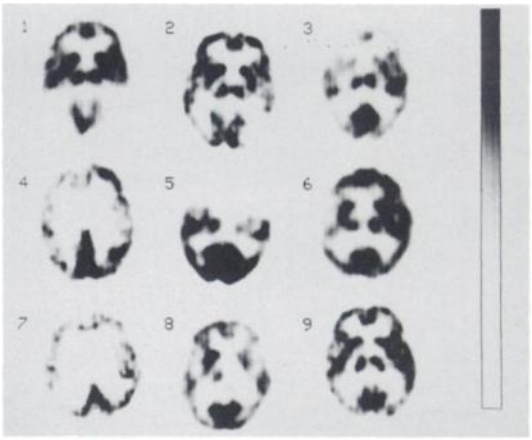

FIGURE 1. Characteristic transverse planes obtained at different (most representative) levels with PET illustrate nine metabolic patterns (glucose metabolism distribution): (1) bilateral temporo-parietal hypometabolism; (2) unilateral temporo-parietal involvement; (3) frontal hypometabolism exceeding temporo-parietal involvement; (4) unilateral frontal hypometabolism exceeding unilateral temporo-parietal involvement; (5) isolated bilateral frontal involvement; (6) left perisylvian hypometabolism; (7) diffuse cortical hypometabolism; (8) multiple cortical and subcortical hypometabolic foci; and (9) normal distribution.

Other scans showed variable distribution of cortical and/or subcortical metabolic impairment (not illustrated).

Scans were first read with the reader blind to clinical data apart from suspicion of dementia. CT scan results were used to address classification concerns, mainly to exclude cerebral infarct. In follow-up studies, the first PET scan served for visual analysis, but all clinical data were used for the final diagnosis.

RESULTS

Table 1 shows the distribution of the population according to final diagnosis and metabolic pattern. We restricted our analysis to both groups with sufficient numbers of patients: probable and definite Alzheimer's disease and degenerative dementia with possible but atypical AD. Tables 2, 3 and 4 detail the distribution of PET patterns according to severity of dementia, age at onset and dementia duration of Alzheimer's disease. Table 5 reports follow-up studies of metabolic patterns in patients who presented with clinical diagnostic difficulties or peculiarities. Table 6 emphasizes the distribution of PET patterns according to severity of dementia in patients with degenerative dementia atypical for AD (DEM).

TABLE 1
Population: Clinical Diagnosis and PET Patterns

	No. of patients	PET pattern of metabolic decrease: TP bilateral	TP unilateral	F > TP bilateral	F > TP unilateral	F bilateral	Left perisylvian	Diffuse cortical	Multifocal	Normal pattern	Other patterns
Final diagnosis											
Alzheimer's disease	65	43***	13*	3	2*	2	—	—	—	2	—
Degenerative dementia atypical for AD	19	2	—	2	—	14**	1*	—	—	—	—
Parkinson's disease and dementia	13	11	—	2	—	—	—	—	—	—	—
Progressive supranuclear palsy	1	—	—	—	—	1	—	—	—	—	—
Vascular dementia	8	1	2	—	—	1	—	—	3	—	1
Mixed dementia	9	5	3	—	—	1	—	—	—	—	—
Creutzfeldt-Jakob disease	3	1*	—	1*	—	—	—	—	—	—	1*
Metachromatic leucodystrophy	1	—	—	—	—	—	—	—	—	—	1*
Dementia from anoxia	1	—	—	—	—	—	—	—	—	—	1
Primary progressive aphasia	2	—	—	—	—	—	2	—	—	—	—
Normal pressure hydrocephalus	3	—	—	—	—	—	—	3	—	—	—
Depression	4	—	—	—	—	—	—	—	—	4	—

Each asterisk corresponds to one neuropathologically proven case.
PET pattern: TP = temporo-parietal involvement; F > TP = frontal greater than temporo-parietal involvement; F = frontal involvement.

Probable and Definite AD

Five presenile patients had histologically proven (definite) Alzheimer's disease (Table 2 and 3). Three who suffered from severe dementia had a characteristic bilateral temporo-parietal hypometabolism and one with mild dementia had unilateral temporo-parietal involvement. The fifth patient with moderate dementia had unilateral frontal hypometabolism more important than ipsilateral temporo-parietal involvement (Fig. 1). This patient was 63 yr old and had a 1-yr history of memory and orientation problems. He also has behavior and judgment problems. Frontal biopsy shows an important congophilic (amyloid) angiopathy, fibrillar gliosis in the cortex and white matter, atrophic neurones with neurofibrillary degeneration and neuritic plaques, but no Pick's cells. Another patient with clinically probable AD and an initial right predominant frontal involvement later showed a typical bilateral temporo-parietal pattern (Fig. 2). He was 58 yr old and had suffered from memory problems for 4 yr. He had mild dementia, lacked initiative, and had impaired social and professional judgment. Three years later, he had orientation problems, aphasia, apraxia, agnosia and he was moderately demented (Table 5, AD3).

In the overall group with probable AD (n = 65), 97% of the PET scans were abnormal (Table 1).

Two patients had normal metabolic distribution (Tables 2 and 3): a 64-yr-old woman with a 1-yr history of memory impairment, orientation problems and apraxia, had mild dementia; a man with a 4-yr history of isolated memory problems had questionable dementia. When he was reexamined 5 yr later, he had mild dementia with apraxia, mild anomia and agnosia. His PET scans showed typical bilateral temporo-parietal hypometabolism (Fig. 3 and Table 5, AD1).

If the first four PET patterns seen in Table 1 are suggestive of probable AD, then the sensitivity of this technique

TABLE 2
Alzheimer's Disease: Severity of Dementia and PET Patterns

Alzheimer's disease	No. of patients	PET pattern of metabolic decrease: TP bilateral	TP unilateral	F > TP bilateral	F > TP unilateral	F bilateral	Normal pattern
Mild	16	8	4*	1	1	—	2
Moderate	25	16	6	1	1*	1	—
Severe	24	19***	3	1	—	1	—

Each asterisk corresponds to one neuropathologically proven case.
Mild AD, age = 65.1 ± 6.7 yr, duration = 3.4 ± 2.9 yr; MMSE (n = 9) = 26.2 ± 2.8 (MMSE, (*23*)).
Moderate AD, age = 68.9 ± 7.2 yr, duration = 2.0 ± 1.3 yr, MMSE (n = 14) = 16.6 ± 4.1.
Severe AD, age = 63.5 ± 7.2 yr, duration = 2.5 ± 1.3 yr, MMSE (n = 4) nonreliable.
PET pattern: TP = temporo-parietal; F > TP = frontal greater than temporo-parietal involvement; F = frontal.

TABLE 3
Alzheimer's Disease: Age at Onset of Dementia and PET Patterns

Onset of AD	No. of patients	PET pattern of metabolic decrease: TP bilateral	TP unilateral	F > TP bilateral	F > TP unilateral	F bilateral	Normal pattern
Before 65 yr	36	22***	6*	2	2*	2	2
65 yr and after	29	21	7	1	—	—	—

Each asterisk corresponds to one neuropathologically proven case.
Age at onset = 58.3 ± 4.5 yr, duration = 2.9 ± 2.2 yr, severity = 2.2 ± 0.8 (Clinical Dementia Rating, (*12*)).
Age at onset = 70.2 ± 5.6 yr, duration = 1.9 ± 1.1 yr, severity = 2.0 ± 1.2.
PET pattern: TP = temporo-parietal; F > TP = frontal greater than temporo-parietal involvement; F = frontal.

for detecting AD is 94%. The sensitivity of characteristic bilateral temporo-parietal involvement for detecting probable AD is 66%. The metabolic patterns in AD are thus quite heterogeneous. Unilateral metabolic impairment occurs in 23% of patients independent of severity of dementia (Table 2) or age at onset of AD (Table 3). The metabolic pattern is not dependent on the duration of dementia in a population (Table 4) but the pattern of individual patients with AD tends to evolve to characteristic bilateral temporo-parietal hypometabolism on follow-up studies (Table 5).

PET's specificity using the characteristic pattern is 68%, and the proportion of nonAD patients without the first four suggestive patterns in Table 1 is 53%. The positive predictive value of PET is then 65%. The poor specificity and positive predictive value reflect a bias of clinical selection in our population (see Discussion).

Two subjects with a clinical diagnosis of AD have isolated bilateral frontal hypometabolism more suggestive of "frontal type dementia" (*24*) (Tables 2 and 3). One patient, a 63-yr-old male, had memory impairment and orientation difficulties for 2 yr as well as behavior problems. He exhibited constructive apraxia and impaired calculation. He was severely demented and could not perform formal frontal testing, but his electroencephalographic recordings were normal. The other patient, a 62-yr-old woman, had moderate dementia with a 1-yr history of memory loss and mild orientation difficulties. She lacked initiative and interest, but was always pleasant. She exhibited constructive apraxia. She had reduced verbal fluency but she normally drew alternating graphical sequences. The diagnosis of frontal-type dementia was not kept before PET. Although both patients may have the disorder, a definite diagnosis is missing.

Degenerative Dementia's with Possible but Atypical AD

Two subjects with degenerative dementia atypical for AD (DEM) had a definite diagnosis of Pick's disease, with ballooned cells and Pick's bodies as histopathological criteria (Table 6). One subject was severely demented and has a bilateral frontal pattern. The other initially suffered from progressive aphasia and exhibited initial left perisylvian (and mainly temporal) hypometabolism, later evolving to bilateral frontal and anterior temporal involvement (Table 5, DEM1, and Table 6). Another patient with bilateral frontal pattern and moderate dementia had a histologically proven diagnosis of progressive subcortical gliosis (Table 6).

The majority of DEM patients (74%) have predominant frontal hypometabolism even at mild stages, but four (21%) have a metabolic distribution similar to that observed in probable AD that is unrelated to the severity of dementia (Table 6).

On the other hand, the population of patients with bilateral frontal hypometabolism is heterogeneous (Table 1),

TABLE 4
Alzheimer's Disease: Disease Duration and PET Patterns

Alzheimer's disease duration	No. of patients	PET pattern of metabolic decrease: TP bilateral	TP unilateral	F > TP bilateral	F > TP unilateral	F bilateral	Normal pattern
Less than 3 yr	37	24*	8	1	1*	2	1
3 yr and more	28	19**	5*	2	1	—	1

Each asterisk corresponds to one neuropathologically proven case.
Disease duration less than 3 yr, age = 66.6 ± 7.7 yr, severity = 2.2 ± 0.7 (Clinical Dementia Rating, (*12*)).
Disease duration more than 3 yr, age = 64.9 ± 6.9 yr, severity = 2.0 ± 0.9.
PET pattern: TP = temporo-parietal; F > TP = frontal greater than temporo-parietal involvement; F = frontal.

TABLE 5
Metabolic Patterns on Follow-up Studies

Patient no.	First scan: Dementia severity	First scan: PET pattern	Delay (months)	Last scan: Dementia severity	Last scan: PET pattern
AD1	Questionable	Normal	62	Mild	Bilateral TP
AD2	Mild	Unilateral TP	48	Moderate	Bilateral TP
AD3	Mild	Unilateral F > TP	36	Moderate	Bilateral TP
AD4	Mild	Bilateral TP	12	Mild	Bilateral TP
AD5	Mild	Bilateral TP	16	Moderate	Bilateral TP
AD6	Mild	Bilateral TP	20	Moderate	Bilateral TP
AD7	Moderate	Bilateral TP	14	Moderate	Bilateral TP
AD8	Moderate	Bilateral TP	65	Severe	Bilateral TP
AD9	Moderate	Bilateral TP	13	Moderate	Bilateral TP
AD10	Severe	Unilateral TP	26	Severe	Bilateral TP
DEM1	Mild	Left perisylvian	22	Severe	Bilateral F
DEM2	Mild	Bilateral F	24	Severe	Bilateral F
DEM3	Moderate	Bilateral F	6	Severe	Bilateral F
VD1	Mild	Multifocal	10	Mild	Multifocal
VD2	Mild	Unilateral TP	34	Moderate	Unilateral TP
VD3	Moderate	Unilateral TP	60	Moderate	Unilateral TP
PPA	—	Left perisylvian	8	—	Left perisylvian
DEP	—	Normal	29	—	Normal

DEM = degenerative dementia atypical for AD; VD = vascular dementia; PPA = primary progressive aphasia; DEP = depression; TP = temporo-parietal; F = frontal.

and apart from cortical degenerative dementia, this group is comprised of patients with PSP or vascular dementia.

DISCUSSION

Methodology

The major weakness in studies like ours is the small number of histologically proven cases. We could not obtain many neuropathological verifications from our population (12 of 129 subjects), but some patients received a definite diagnosis for disorders other than AD, which attests to the specificity of PET.

"Degenerative dementia" within our population is defined as those patients classified as possible AD who may also be diagnosed with frontal-type dementia (*24,25*). Three patients also had slowly progressive aphasia with subsequent dementia. The diagnosis of DEM was based on historical and clinical evidence of prominent changes in behavior, judgment ability and abstraction capacity, with fluctuating memory loss and lack of spatial disorientation or visuospatial disturbance. Not all patients could perform formal frontal lobe neuropsychological testing (*24*). The ratio of incidence of degenerative dementia atypical for AD-to- probable and definite Alzheimer's disease is 1:3.4 in our population. This probably corresponds to a selection bias because most atypical cases were referred for PET studies. However, the ratio of frontal type dementia-to-AD was estimated at 1:4 in another series (*24*).

Our population is clearly biased to patients for whom

TABLE 6
Degenerative Dementia: Severity and PET Patterns

Degenerative dementia atypical for Alzheimer's disease (DEM)	No. of patients	PET pattern of metabolic decrease: TP bilateral	F > TP bilateral	F bilateral	Left perisylvian
Mild	5	—	—	4	1*
Moderate	8	1	2	5†	—
Severe	6	1	—	5*	—

*Definite Pick's disease.
†Definite progressive subcortical gliosis.
Mild DEM, age = 58.8 ± 5.8 yr, duration = 3.4 ± 1.8 yr.
Moderate DEM, age = 54.9 ± 11.1 yr, duration = 1.7 ± 0.5 yr.
Severe DEM, age = 66.3 ± 10.9 yr, duration = 3.0 ± 2.4 yr.
PET pattern: TP = temporo-parietal; F = frontal.

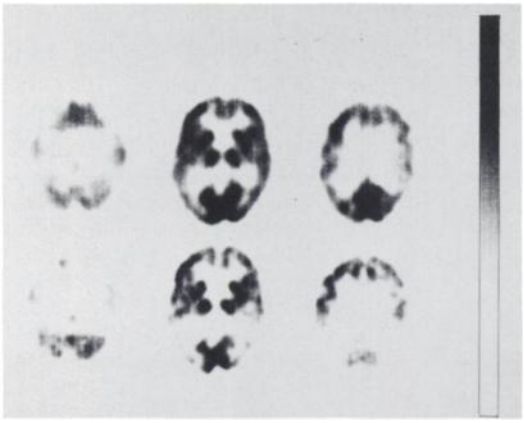

FIGURE 2. The first and second rows correspond to two different PET studies performed at 3-yr intervals in a patient with probable AD. First row: distribution of glucose metabolism illustrated on transverse planes showed interhemispheric asymmetry with unilateral frontal hypometabolism exceeding temporo-parietal involvement. Second row: follow-up study revealed a characteristic pattern of bilateral temporo-parietal hypometabolism with asymmetrical frontal involvement.

functional imaging could be of interest. Controls were not included, and patients with vascular dementia were few because their diagnosis was already obtained from clinical criteria and neuroanatomical imaging. Many Parkinsonian patients, however, were referred for documentation of subsequent dementia.

Sensitivity

Five patients with histologically proven Alzheimer's disease have characteristic or suggestive PET patterns, i.e., temporo-parietal hypometabolism with or without frontal involvement of variable importance. In this study, we considered that hypometabolism in both the anterior and posterior associative cortices is suggestive of AD, even if frontal involvement is more important than temporo-parietal involvement. Neuropathological reports already mentioned the possibility that frontal atrophy be predominant in AD (*26,27*). Unilateral frontal hypometabolism exceeding temporo-parietal involvement was also considered as suggestive of AD. This was later supported by neuropathological confirmation in one patient (Table 2) and by sequential PET studies in another (Fig. 2).

The sensitivity of characteristic and suggestive PET patterns for the clinical diagnosis of probable Alzheimer's disease was 94% in our population. Herholz et al. (*28*) reported a 92% sensitivity for a single metabolic ratio comparing affected to unaffected regions in AD. The ratio, however, does not reflect the metabolic heterogeneity of the disease (*29*), which is useful for a differential diagnosis. In a recent SPECT study (*11*) in a large population (52 patients with AD from 113 patients), the percentage of AD patients showing a pattern of decreased perfusion similar to our characteristic or suggestive categories was 80% (compared to our 94%). A disadvantage for SPECT may be nonlinearity between tracer distribution and cerebral blood flow. We also analyzed calculated metabolic images for better interregional contrast. On the other hand, there should be little difference between perfusion and metabolic studies, since those parameters are coupled in AD (*1*) and formal conclusions could only be determined by a comparison of SPECT and PET studies in the same population.

Temporo-parietal hypometabolism was unilateral in 23% of our patients, regardless of dementia severity. The importance of unilateral involvement for the interpretation of PET images was already emphasized (*7*). After visual analysis of PET cerebral blood flow distribution, Powers et al. (*30*) found characteristic bilateral temporo-parietal hypoperfusion in only 5/13 probable AD patients, but the sensitivity was increased to 11/13 patients if marked asymmetrical pattern was taken into account.

The metabolic pattern was normal in two patients with probable AD (3%) using our NeuroEcat camera, whereas normal flow distribution has been reported in 7.7%–19% of AD patients using SPECT (*29,3*). Measurement of hippocampal hypometabolism with new tomographs and better resolution should provide earlier data for patients with slowly progressive memory loss (*31*). It would be interesting to know if cases of dementia without significant brain neuropathological findings (*32*) might have normal metabolism in vivo; this group of subjects requires further investigation (*33*).

The sensitivity of clinical diagnosis for AD is already 70%–90% (*34–36*). Functional imaging, however, gives further arguments for differential diagnosis (*3*). Isolated bilateral frontal hypometabolism is probably the main noncharacteristic pattern observed in probable AD. In the absence of temporo-parietal involvement, it may suggest alternative, nonAlzheimer neuropathology (*37,24*), especially in presenile-onset cases (*38*).

Specificity

Most patients with degenerative dementia atypical for AD have bilateral frontal hypometabolism. However, as expected in patients who do fulfill criteria for possible AD,

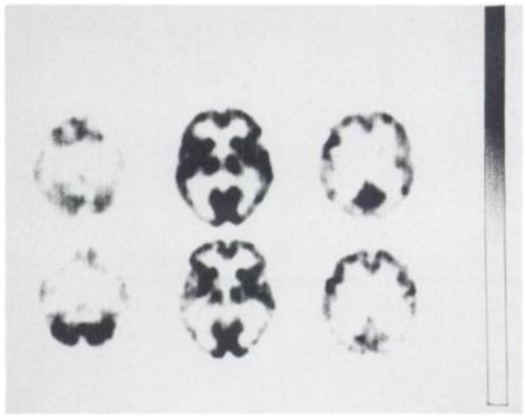

FIGURE 3. The first and second rows correspond to two different PET studies performed at 5-yr intervals in a patient with probable AD. First row: distribution of glucose metabolism illustrated on transverse planes was considered as normal. Second row: follow-up study revealed a characteristic pattern of bilateral temporo-parietal hypometabolism.

a non-negligible proportion of those (21%) have a pattern similar to that observed in probable AD. As already discussed, formal neuropsychological testing for frontal lobe impairment might increase the accuracy of the clinical diagnosis in those patients, but neuropathological confirmation will be essential to draw diagnostic conclusions. Effectively, our neuropathologically proven AD patient with predominant unilateral frontal metabolic pattern had frontal-type dementia. Brun (*27*) observed definite Alzheimer's disease in 2/26 patients with clinical frontal-type dementia. PET may help in distinguishing those patients in vivo (*39*).

Cerebral metabolic distribution in patients with vascular dementia or mixed dementia is sometimes difficult to differentiate from that in AD (*40*). This is also true in the group of Parkinsonian patients with dementia (PPD) (*8*), but the diagnosis in both vascular dementia and PPD is mainly based on clinical data and anatomical imaging. All patients with Parkinson's disease and dementia had a metabolic pattern suggestive of AD with bilateral temporo-parietal involvement, but metabolic impairment was greater in the frontal than in temporo-parietal cortices in two patients (Table 1). We also observed a metabolic pattern suggestive of AD in two patients with Creutzfeldt Jakob disease. However, the rapid clinical evolution and EEG abnormalities were characteristic of the disease.

On the other hand, miscellaneous metabolic patterns cannot be mistaken for others. In one patient with Creutzfeldt Jakob disease, for example, hypometabolic and hypermetabolic foci are distributed all over the brain. In our patient with metachromatic leukodystrophy and dementia from anoxia, metabolism is impaired both in the thalami and cortical areas.

Longitudinal studies

Disease duration was generally relatively short in our study. However, the metabolic pattern evolved when the disease progressed. In degenerative dementias, unilateral hypometabolism observed at the onset of disease frequently becomes bilateral with time, even if interhemispheric asymmetry persists (Table 5). In AD, cognitive troubles may precede metabolic impairments (*41*), which only appear on follow-up studies (Fig. 3). In slowly progressive aphasia with subsequent dementia (three AD and three DEM patients in our population), bilateral metabolic impairment in the temporo-parietal or frontal cortices is observed sooner or later on follow-up studies (Table 5, DEM1). Hypometabolism observed in isolated primary progressive aphasia (*4*), however, remains essentially localized in the left perisylvian area, regardless of disease duration (*42*).

In conclusion, PET studies have demonstrated temporo-parietal hypoperfusion and hypometabolism indicative of AD. If the first PET scan is questionable, longitudinal studies may enable accurate classification of patients referred for differential diagnosis of dementia.

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