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Regional Cerebral Blood Flow Study with ^{123}I -IMP in Patients with Degenerative Dementia

Takashi Ohnishi¹
 Hiroaki Hoshi¹
 Shigeki Nagamachi¹
 Seishi Jinnouchi¹
 Shigemi Futami¹
 Katsushi Watanabe¹
 Yoshio Mitsuyama²

Regional cerebral blood flow was evaluated by single-photon emission CT (SPECT) with ^{123}I -*N*-isopropyl-*p*-iodoamphetamine (^{123}I -IMP) in 11 patients with dementia of the Alzheimer type, three patients with progressive dementia and motor neuron disease, and eight healthy control subjects. Regional blood flow measurements in the bilateral frontal, parietal association, and temporal cortices were lower in the Alzheimer dementia patients than in controls. Flow deficits in the parietal association cortex were demonstrated in all patients with Alzheimer-type dementia; these deficits were correlated with the severity of disease. Lateral hemispheric asymmetry was seen in nine of 11 patients with Alzheimer-type dementia. In all three patients with progressive dementia and motor neuron disease, flow deficits were demonstrated in the bilateral frontal and temporal cortices, but no flow deficits were seen in the parietal association cortex.

Brain SPECT with ^{123}I -IMP may be useful in the differential diagnosis and evaluation of the severity of degenerative dementia.

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One of the most common problems associated with aging is dementia. Its prevalence in people over 65 years old has been estimated to be 4-5%; approximately 50% of cases in the United States are attributed to dementia of the Alzheimer type (DAT) [1]. The most common cause of dementia in Japan is multiinfarct dementia, which accounts for 60% of cases [2]. The second leading cause of dementia in Japan is DAT, occurring in 30% of cases [2]. The prevalence of patients with DAT has been increasing [2].

Positron emission tomographic (PET) studies have described regional cerebral blood flow (rCBF) and metabolism in DAT and Alzheimer disease. PET is an expensive and difficult technique for routine use, and other methods of physiologic imaging that might be appropriate for wide-scale clinical application have been sought. Single-photon emission CT (SPECT) uses radionuclides of the sort currently used in routine clinical nuclear medicine studies. Single-photon emitting radiopharmaceuticals that are capable of measuring cerebral function have been developed and are commercially available. One such tracer, *N*-isopropyl-*p*-iodoamphetamine (IMP), labeled with iodine-123, crosses the blood-brain barrier and binds to non-specific high-capacity binding sites [3]. ^{123}I -IMP is distributed in the brain in proportion to blood flow, and when scanned tomographically can provide three-dimensional information about rCBF [3]. We report the usefulness of ^{123}I -IMP SPECT imaging to evaluate degenerative dementia (DAT and progressive dementia with motor neuron disease [MND]).

Subjects and Methods

A total of 22 right-handed patients were investigated (Table 1). Eleven patients with DAT met the criteria of the third edition of the American Psychiatric Association's *Diagnostic and Statistical Manual* [4] for primary degenerative dementia. They also met the criteria of the

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¹ Department of Radiology, Miyazaki Medical College, 5200 Ohaza Kihara, Kiyotake, Miyazaki-gun Miyazaki-ken, 889-16 Japan. Address reprint requests to T. Ohnishi.

² Department of Psychiatry, Miyazaki Medical College, Miyazaki-ken, 889-16 Japan.

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TABLE 1: Breakdown of Patients by Diagnostic Category

Diagnostic Category	No. of Cases	Mean Age
Dementia of Alzheimer type	11	66
Progressive dementia with motor neuron disease	3	52
Controls	8	64
Total	22	

National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association for probable Alzheimer disease [5]. The disease courses in these patients were considered typical of Alzheimer disease, with insidious onset, progression of memory loss, and disorders of language and visual/spatial relations.

The diagnosis of progressive dementia with MND was based on the criteria of Mituyama et al. [6]. Symptoms in these patients were atypical for Alzheimer disease. They had memory loss, personality change, loss of spontaneous speech, and disorders of motor neurons. Memory loss was mild in these patients. Other causes of dementia were excluded by standard methods, including CT, MR imaging, and electroencephalography. The eight normal control subjects were 53–76 years old (mean age, 64 years).

Neuropsychological testing was performed in all patients by using Hasegawa's Dementia Score (HDS) as a measure of disease severity [7]. An HDS score of 22–30.5 reflected mild dementia, a score of 10.5–21.5 reflected moderate dementia, and a score of 0–10 reflected severe dementia. Two of 11 patients with DAT had mild dementia, two had moderate dementia, and seven patients had severe dementia. All patients with progressive dementia with MND had mild dementia.

Methods

^{123}I -IMP SPECT studies were performed by using 111 MBq (3 mCi) of ^{123}I -IMP with a ring-type gamma camera (SET-031, Shimadzu Co., Kyoto, Japan), which consists of a gantry assembly with 64 scanning

detectors. This system has three rings and simultaneously acquires six parallel slices with a center-to-center interslice gap of 17 mm. A high-resolution collimator was used. The raw data were reconstructed by filtered back projection by using a Romachan-Butterworth filter. Filter order was 8 and cutoff frequency was 28 mm. Reconstruction was performed by using a Data General ECLIPSE S-120 processor for a 64×64 matrix image. Slice thickness was 16 mm. Data acquisition started 30 min after IV injection of 111 MBq of ^{123}I -IMP and lasted until 600,000 counts were collected. The tomographic images were obtained at 0, 17, 35, 52, 70, and 87 mm above the orbitomeatal plane. The full width at half maximum was 15 mm in the center of the gantry by phantom study.

A semiquantitative method of assessing regional variation was used; regional tracer uptake was measured in circular (20 mm^2) regions of interest (ROIs) over right and left frontal association, parietal association, temporal, perirolandic, and occipital (primary visual cortex) cortical regions; basal ganglia; and cerebellar hemispheres (Fig. 1). Anatomic localization of the various ROIs on IMP SPECT was determined by CT or MR. IMP uptake was expressed as the cerebrum/cerebellum activity ratio (C/C ratio), a ratio of the activity in cerebral ROIs to the activity in the cerebellar ROI. The cerebellum was chosen as the control region for assessing uptake because it is not known to be a site of primary abnormality in degenerative dementia [8, 9], and cerebellar atrophy was not seen on CT or MR in any patient. The ratios for patients with dementia were compared with those for the control group. Student's *t* test for nonpaired samples was used for analysis of the results obtained for each of these groups. Lateral hemispheric asymmetry was evaluated by an asymmetry index (AI). This was calculated from the C/C ratio: $[\text{AI} = 1 + (\text{C/C ratio in right region} - \text{C/C ratio in left region}) / (\text{C/C ratio in right region} + \text{C/C ratio in left region})]$. We decided that lateral hemispheric asymmetry was present when the AI in patients deviated by more than 2 SD from that of controls.

Results

Control Subjects

C/C ratios and asymmetry indexes in controls are shown in Table 2. C/C ratios ranged from 0.84 to 0.95. There was a

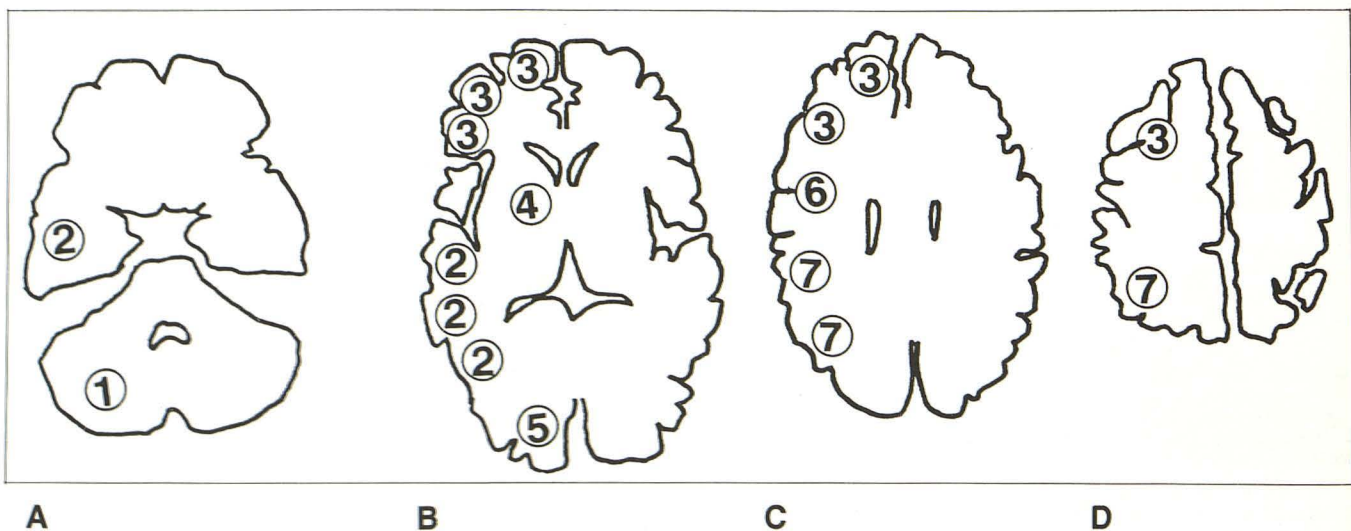


Fig. 1.—Regions of interest in each brain slice.

A, 17 mm above orbitomeatal plane.

B, 52 mm above orbitomeatal plane.

C, 70 mm above orbitomeatal plane.

D, 87 mm above orbitomeatal plane.

1 = cerebellum, 2 = temporal cortex, 3 = frontal association cortex, 4 = basal ganglia, 5 = occipital cortex, 6 = perirolandic area, 7 = parietal association cortex.

TABLE 2: Cerebrum/Cerebellum Activity (C/C) Ratios in Control Subjects, Patients with Dementia of the Alzheimer Type, and Patients with Progressive Dementia (PD) with Motor Neuron Disease (MND)

Region/Side	Mean CC Ratio \pm 1 SD				PD with MND (n = 3)
	Controls (n = 8) [Asymmetry Index] ^a	All Patients (n = 11)	Mild or Moderate (n = 4)	Severe (n = 7)	
Frontal					
Right	0.86 \pm 0.06 [1.00 \pm 0.03]	0.70 \pm 0.18 ^b	0.87 \pm 0.05	0.60 \pm 0.15 ^c	0.63 \pm 0.05 ^c
Left	0.84 \pm 0.10	0.69 \pm 0.16 ^b	0.87 \pm 0.02	0.58 \pm 0.11 ^c	0.59 \pm 0.07 ^d
Temporal					
Right	0.89 \pm 0.04 [1.00 \pm 0.04]	0.72 \pm 0.14 ^e	0.84 \pm 0.08	0.65 \pm 0.11 ^c	0.69 \pm 0.01 ^c
Left	0.86 \pm 0.09	0.65 \pm 0.13 ^d	0.79 \pm 0.08	0.57 \pm 0.05 ^c	0.68 \pm 0.01 ^e
Perirolandic					
Right	0.84 \pm 0.09 [0.99 \pm 0.05]	0.89 \pm 0.03	0.89 \pm 0.03	0.89 \pm 0.03	0.84 \pm 0.02
Left	0.88 \pm 0.08	0.89 \pm 0.03	0.89 \pm 0.02	0.89 \pm 0.04	0.89 \pm 0.02
Parietal					
Right	0.91 \pm 0.06 [1.01 \pm 0.04]	0.63 \pm 0.10 ^c	0.73 \pm 0.04 ^c	0.57 \pm 0.07 ^c	0.91 \pm 0.03
Left	0.89 \pm 0.07	0.60 \pm 0.11 ^c	0.69 \pm 0.02 ^c	0.54 \pm 0.09 ^c	0.89 \pm 0.03
Basal ganglia					
Right	0.86 \pm 0.07 [0.98 \pm 0.03]	0.87 \pm 0.04	0.85 \pm 0.03	0.87 \pm 0.03	0.83 \pm 0.01
Left	0.89 \pm 0.09	0.91 \pm 0.03	0.92 \pm 0.02	0.91 \pm 0.04	0.88 \pm 0.03
Occipital					
Right	0.95 \pm 0.05 [1.00 \pm 0.01]	0.94 \pm 0.03	0.95 \pm 0.04	0.94 \pm 0.01	0.96 \pm 0.06
Left	0.95 \pm 0.06	0.94 \pm 0.05	0.96 \pm 0.02	0.93 \pm 0.05	0.96 \pm 0.02

^a Asymmetry index = 1 + (right side - left side)/(right side + left side).

^{b-e} By Student's t test for nonpaired samples, ^b $p < .05$, ^c $p < .001$, ^d $p < .002$, and ^e $p < .01$ compared with controls.

tendency for the primary visual cortex to show slightly elevated IMP uptake. AIs ranged from 0.98 to 1.01. The distribution of activity in the controls was symmetric and homogeneous in the cortex and basal ganglia with no site of reduced uptake (Fig. 2).

DAT

The C/C ratios in patients with DAT and control subjects are shown in Table 2. The C/C ratios for the DAT patients were significantly lower than those for controls in the right frontal association cortex (0.86 vs 0.70, $p < .05$), left frontal

association cortex (0.84 vs 0.69, $p < .05$), right temporal cortex (0.89 vs 0.72, $p < .01$), left temporal cortex (0.86 vs 0.65, $p < .002$), right parietal association cortex (0.91 vs 0.63, $p < .001$), and left parietal association cortex (0.89 vs 0.60, $p < .001$). IMP SPECT in patients having mild or moderate dementia did not show reduced IMP uptake in the bilateral frontal association and temporal cortices, but reduced IMP uptake was seen in those regions in patients with severe dementia (right frontal, 0.60 [$p < .001$]; left frontal, 0.58 [$p < .001$]; right temporal 0.65 [$p < .001$]; left temporal, 0.57 [$p < .001$]). The C/C ratios in both parietal association cortices were significantly lower in patients with mild to severe

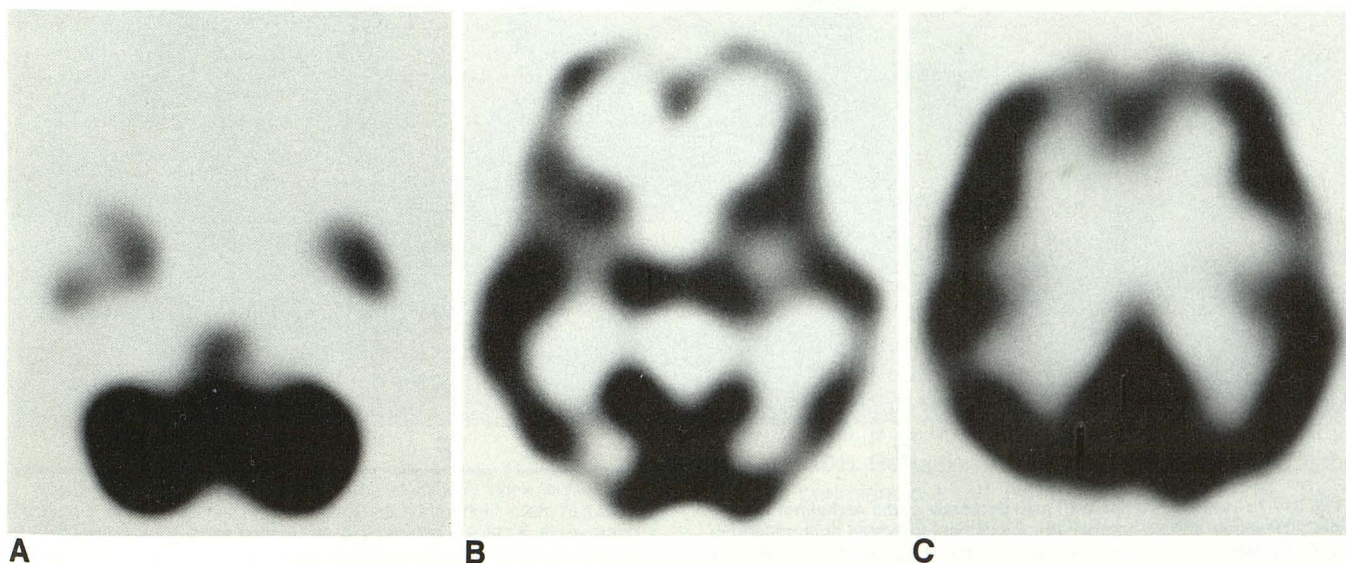


Fig. 2.—83-year-old healthy man with no evidence of dementia.

A-C, ¹²³I-IMP SPECT shows symmetric, homogeneous uptake in cortical regions and basal ganglia with no areas of reduced uptake.

dementia than in controls ($p < .001$, Table 2). Furthermore, the C/C ratios in the parietal association cortex were significantly lower in patients with severe dementia than in patients with mild or moderate dementia (right parietal, 0.73 vs 0.57 [$p < .001$]; left parietal 0.69 vs 0.54 [$p < 0.02$]). The periorlandic area, basal ganglia, and occipital cortex did not show reduced IMP uptake in patients with DAT. IMP SPECT studies in patients with mild dementia showed bilateral reduced uptake in the parietal region, but there was no other site of decreased uptake (Fig. 3). Reduced IMP uptake was seen in bilateral frontal, parietal association, and temporal cortices in patients with severe dementia (Fig. 4). Lateral hemispheric asymmetry was seen in nine of 11 patients with DAT. Asymmetry was present in all six patients who were less than 65 years old at the time of disease onset and in three of five

patients in whom onset occurred after 65 years of age. Regional asymmetry in IMP uptake in DAT is summarized in Table 3. Lateral asymmetries were observed in the frontal, parietal association, and temporal cortices, where there was reduced IMP uptake in DAT patients. The relationship between lateral asymmetry and clinical features is shown in Table 4. Memory disorder, visual/spatial disorientation, dressing apraxia, and constructional apraxia were observed in all groups (right < left, right > left, and right = left). Aphasia, dysgraphia, and Gerstmann syndrome were observed more often in right > left cases than in other groups. Figure 5 shows IMP SPECT images in a DAT patient with aphasia and Gerstmann syndrome. The IMP SPECT study shows significant hypoperfusion in the left hemisphere, particularly in the temporal and parietal regions.

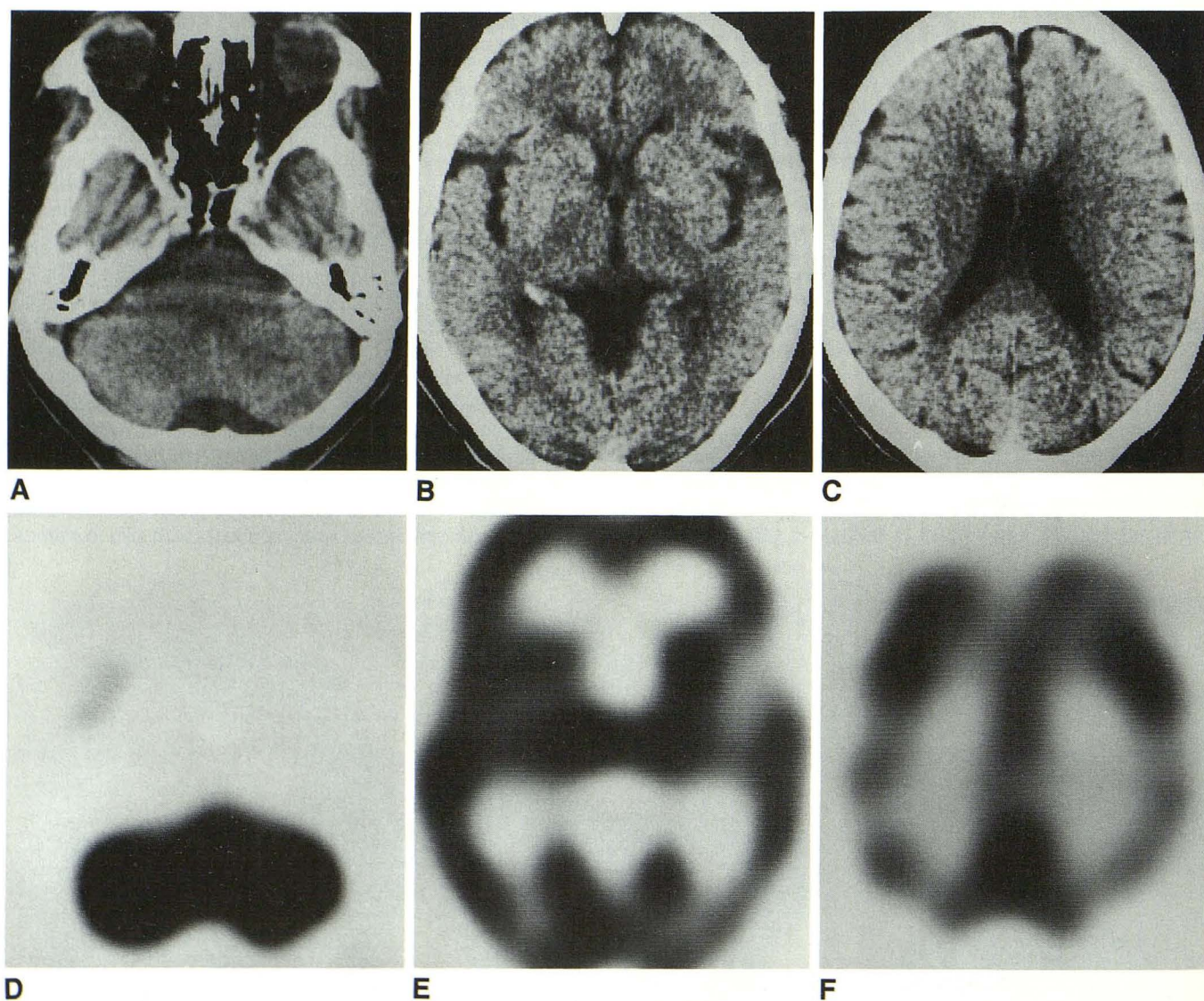


Fig. 3.—73-year-old woman with mild dementia of the Alzheimer type.

A–C, CT shows diffuse cortical atrophy without localized abnormality.

D–F, ^{123}I -IMP SPECT shows bilateral reduced uptake in parietooccipital regions (D) with no other sites of reduced uptake.

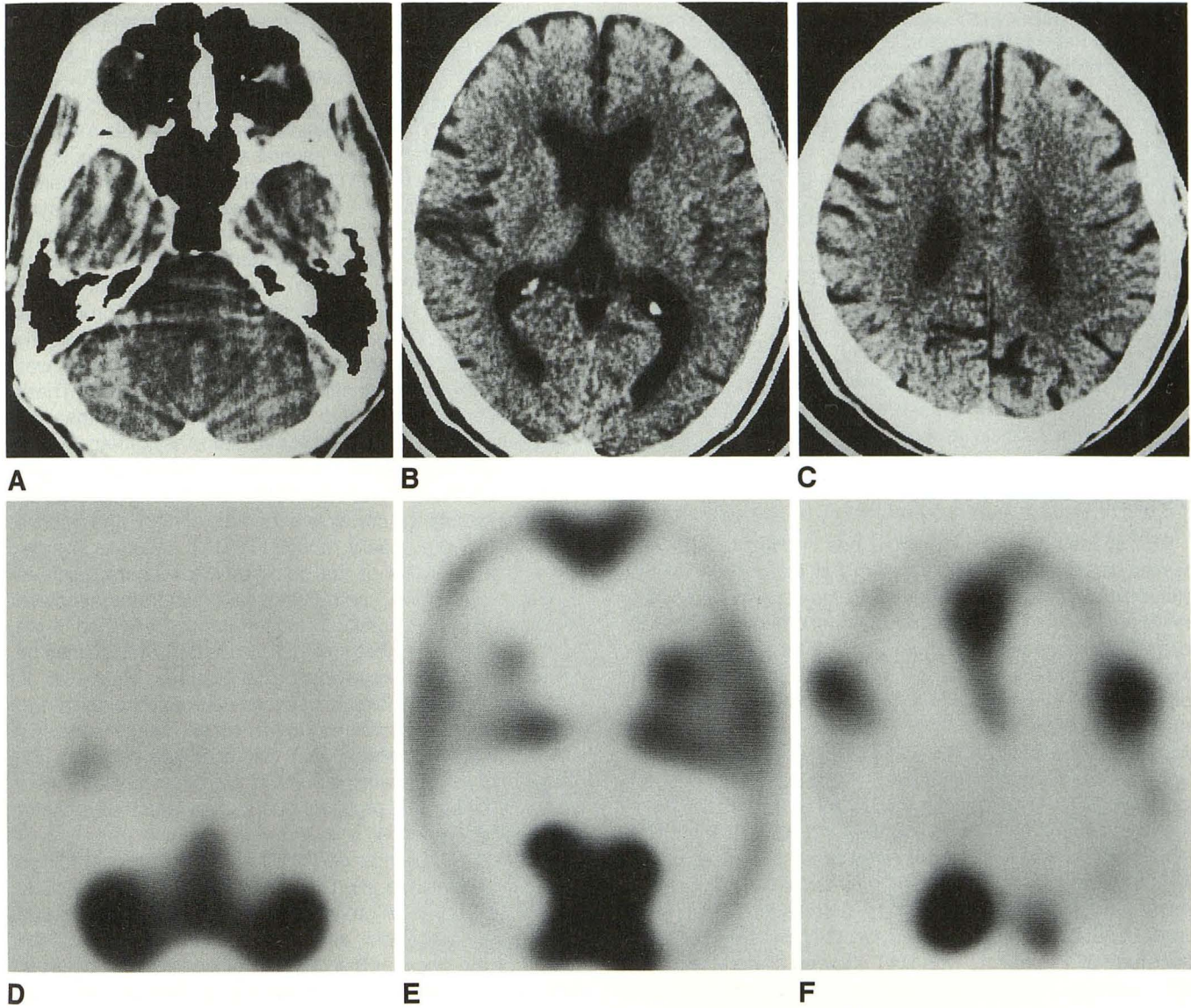


Fig. 4.—51-year-old man with severe dementia of the Alzheimer type and visual/spatial disorientation. A–C, CT shows diffuse cortical atrophy but no localized abnormality. D–F, ¹²³I-IMP SPECT shows bilateral reduced uptake in frontal, temporal, and parietal regions (E and F).

TABLE 3: Asymmetry of ¹²³I-IMP Uptake in Patients with Dementia of the Alzheimer Type

Region	No. of Patients (n = 11)		
	Right > Left	Right < Left	Right = Left
Frontal	4	1	6
Temporal	4	2	5
Perirolandic	0	0	11
Parietal	3	3	5
Basal ganglia	0	0	11
Occipital	0	0	11

Note.—Asymmetry was assessed by the asymmetry index (AI [see text]). For right > left, AI (patients) > AI (controls) + 2 SD; for right < left, AI (patients) < AI (controls) - 2 SD; for right = left, AI (controls) - 2 SD ≤ AI (patients) ≤ AI (controls) + 2 SD.

Progressive Dementia with MND

The C/C ratios in patients with progressive dementia and MND are shown in Table 2. These patients had mild dementia. The C/C ratios for progressive dementia with MND were significantly lower than those for controls in the right frontal association cortex (0.86 vs 0.63, *p* < .001), left frontal association cortex (0.84 vs 0.59, *p* < .002), right temporal cortex (0.89 vs 0.69, *p* < .001), and left temporal cortex (0.86 vs 0.68, *p* < .01). Reduction in IMP uptake was not found in the bilateral perirolandic areas, parietal association cortex, basal ganglia, and occipital cortex. Lateral asymmetry was not studied in these patients, because only three patients had

TABLE 4: Relationship Between Asymmetry and Clinical Features in Patients with Dementia of the Alzheimer Type

Clinical Feature	¹²³ I-IMP Uptake (n = 11)		
	Right > Left (n = 5)	Right < Left (n = 4)	Right = Left (n = 2)
Memory disorder	5	4	2
Visual/spatial disorientation	2	3	1
Dressing apraxia	3	3	1
Constructional apraxia	1	2	0
Aphasia	4	1	0
Dysgraphia	3	1	0
Gerstmann syndrome	3	0	0

this disease. The characteristic appearance of the disease is moderate reduced IMP uptake in the anterior hemisphere without marked cortical atrophy (Fig. 6).

Discussion

PET studies using ¹⁸F-deoxyglucose in patients with Alzheimer disease have demonstrated that the severity of the metabolic abnormality correlates with the severity of disease as determined by clinical and psychometric testing [10]. Deficits of tracer uptake in the temporoparietal and frontal cortices of DAT patients have been reported with the use of PET with O-15, ¹⁸F-deoxyglucose to assess rCBF, oxygen utilization, and glucose metabolism. PET is a useful method to diagnose and evaluate DAT patients [10–14]. SPECT is an emission tomographic technique that, unlike PET, does not require a nearby cyclotron for production of radiopharmaceuticals. Therefore, greater availability and lower cost make SPECT a technique of potentially greater clinical utility. SPECT studies using ¹²³I-IMP or ^{99m}Tc-hexamethylpropyleneamine oxime (^{99m}Tc-HM-PAO) show decreased rCBF in temporal, parietal, and frontal cortices in DAT patients [15–22]. Our study of 11 patients with DAT showed bilateral reduced IMP uptake in the parietal association cortex, the degree of

reduction reflecting the severity of disease. Reduced IMP uptake in the parietal association cortex seemed to be a characteristic finding in patients in the early stages of DAT. Reduced IMP uptake in the frontal association and temporal cortices was found in patients with severe dementia. We think that the flow deficit in the parietal association cortex is the most sensitive marker of DAT. Lateral hemispheric asymmetry was seen in nine of 11 patients with DAT. Lateral asymmetries in hemispheric cerebral glucose metabolic rates have been reported. Koss et al. [23] studied Alzheimer patients who had been divided into two groups on the basis of age. The asymmetric glucose utilization in the temporoparietal cortex was similar for patients older than 65 years and elderly controls. Right temporoparietal cortex hypometabolism was seen in seven of 11 patients who were under 65 years. These seven patients were found to be more demented than the four younger patients. We think that lateral asymmetry in DAT patients can be correlated with clinical features, since it was seen in the parietal association cortex, frontal association cortex, and temporal cortex, where rates of rCBF and glucose metabolism were usually reduced in DAT patients. The patients with disorders of the dominant hemisphere, such as aphasia, dysgraphia, and Gerstmann syndrome, showed more reduced IMP uptake in the left hemisphere than in the right. This suggests that flow deficits on IMP SPECT may be associated with neuropsychological features. Haxby et al. [24] studied the relationship between neuropsychological and cerebral metabolic asymmetry in Alzheimer disease using PET with FDG. They reported that discrepancies between language and visual/spatial deficits in Alzheimer disease were associated with, and probably due to, this lateral asymmetry of metabolic reduction.

Progressive dementia with MND is a new clinicopathologic category of dementia [6]. The characteristic features include (1) the slow onset of progressive dementia in the presenile period; (2) neurogenic muscular deterioration during the course of the illness; (3) a duration of illness, from onset to death, of 1–3 years; (4) the absence of extrapyramidal symp-

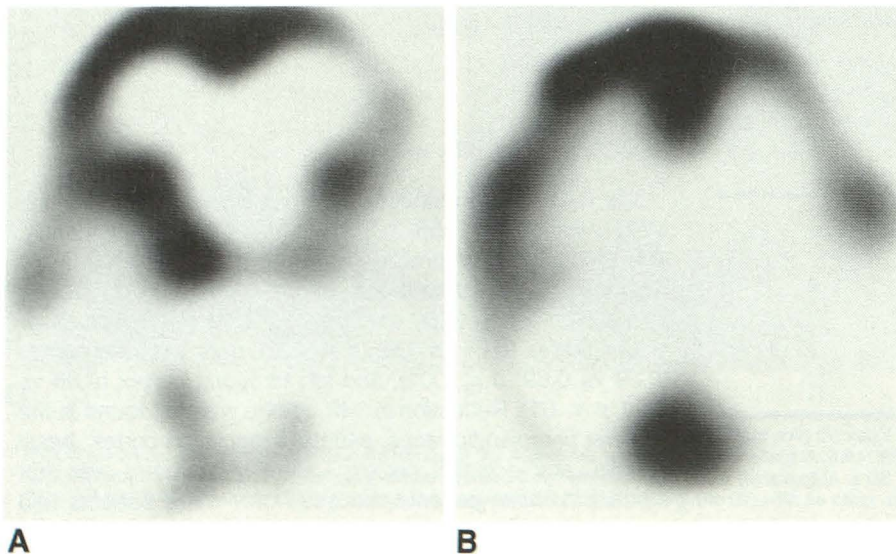


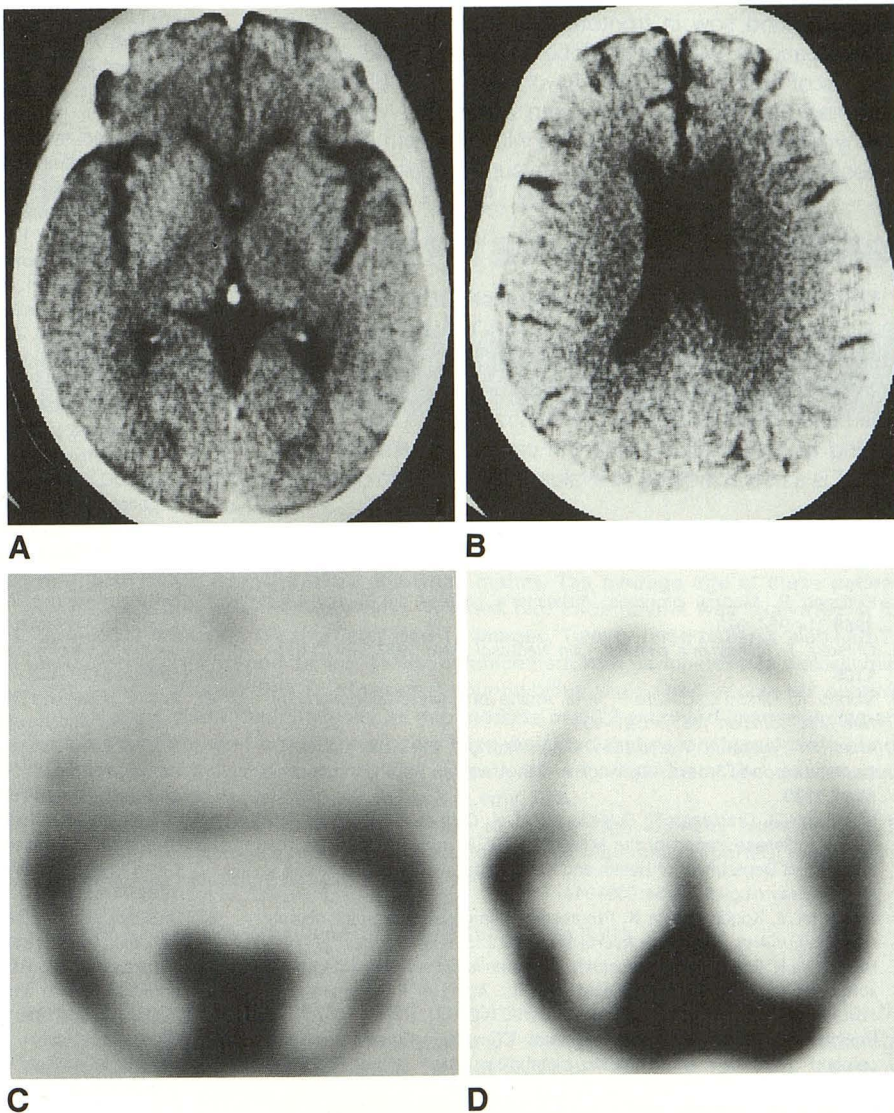
Fig. 5.—58-year-old woman with moderate dementia of the Alzheimer type, aphasia, and Gerstmann syndrome. MR showed diffuse cortical atrophy.

A and B, ¹²³I-IMP SPECT shows significant hypoperfusion in left hemisphere, particularly in temporal and parietal regions.

Fig. 6.—52-year-old woman with mild progressive dementia with motor neuron disease and bulbar palsy.

A and B, CT shows mild cortical atrophy in frontal and temporal lobes.

C and D, ^{123}I -IMP SPECT shows bilateral reduced uptake in frontal and temporal regions.



toms and definite sensory deficits; (5) the absence of characteristic abnormalities in the CSF or on electroencephalography; (6) no known parental consanguinity or familial occurrence; and (7) nonspecific, mild degenerative changes throughout the CNS without evidence of cerebrovascular disease or primary degenerative dementia, but with the presence of pathologic findings of MND [4, 25]. The main mental symptoms include global intellectual impairment, dysfunctional memory, personality change, emotional illness, and loss of spontaneous speech [4, 26]. The symptoms of this unique syndrome have usually been interpreted as unclassified presenile dementia. The absence of any neuropathologic evidence of other disease suggested that progressive dementia with MND was etiologically different from classical amyotrophic lateral sclerosis (ALS), Pick disease, and DAT [4, 26]. Our IMP SPECT study in progressive dementia with MND showed reduced uptake in the frontal and temporal regions without reduction in IMP uptake in the parietal association cortex. These findings were similar to those of Pick disease

and progressive supranuclear palsy, but different from those of classical DAT. Previous PET studies of cerebral metabolic rates for glucose in patients with ALS revealed hypometabolism throughout the cortex and basal ganglia, especially in the motor-sensory cortex and putamen [26, 27]. These findings were different from the rCBF pattern on IMP SPECT in patients with progressive dementia and MND. We believe that low perfusion in the anterior cerebral hemisphere is characteristic of progressive dementia with MND, and IMP SPECT may enable the differentiation of progressive dementia with MND from DAT or ALS patients during life. We reported the usefulness of IMP SPECT in patients with this unique syndrome [28] and speculate that reduced IMP uptake in the frontal and temporal cortical regions may be associated with personality change and loss of spontaneous speech. SPECT and $^{99\text{m}}\text{Tc}$ -HM-PAO studies have demonstrated frontal hypoperfusion in patients with symptoms of personality change, apathy, and disinhibition [29]. Studies using the xenon-133 inhalation method to measure rCBF have demonstrated di-

minished blood flow in frontotemporal brain regions in demented patients with frontal lobe syndromes and autopsy changes of Pick disease [30]. Two such cases of autopsy-confirmed Pick disease have been associated with frontal lobe hypometabolism when studied with PET with ^{18}F -deoxyglucose with [31, 32]. These results support our speculation.

Conclusions

IMP SPECT studies show characteristic rCBF patterns in DAT and progressive dementia with MND. We think that IMP SPECT may enable differentiation among groups of degenerative dementia patients during life. The physiologic findings in dementia patients can be demonstrated with IMP SPECT imaging to be correlated with the clinical presentation. IMP SPECT is a useful method to evaluate patients with dementia.

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