Annals of Nuclear Medicine Vol. 16, No. 8, 515–525, 2002

Clinical application of positron emission tomography for diagnosis of dementia

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Clinical applications of PET studies for dementia are reviewed in this paper. At the mild and moderate stages of Alzheimer's disease (AD), glucose metabolism is reduced not only in the parietotemporal region but also in the posterior cingulate and precuneus. At the advanced stage of AD, there is also a metabolic reduction in the frontal region. In AD patients, glucose metabolism is relatively preserved in the pons, sensorimotor cortices, primary visual cortices, basal ganglia, thalamus and cerebellum. In patients with dementia with Lewy bodies, glucose metabolism in the primary visual cortices is reduced, and this reduction appears to be associated with the reduction pattern in AD patients. In patients with frontotemporal dementia, reduced metabolism in the frontotemporal region is the main feature of this disease, but reduced metabolism in the basal ganglia, and/or parietal metabolic reduction can be associated with the frontotemporal reduction. When corticobasal degeneration is associated with dementia, the reduction pattern of dementia is similar to the reduction pattern in AD and the hallmarks of diagnosing corticobasal degeneration associated with dementia are a reduced metabolism in the primary sensorimotor region and/or basal ganglia and an asymmetric reduction in the two hemispheres. FDG-PET is a very useful tool for the diagnosis of early AD and for the differential diagnosis of dementia. I also describe clinical applications of PET for the diagnosis of dementia in Japan.

Key words: positron emission tomography (PET), F-18 fluorodeoxyglucose (FDG), dementia, Alzheimer disease, glucose metabolism

Introduction

AS THE NUMBER of elderly people increase, the number of people with dementia, especially the number of people with degenerative dementia including Alzheimer's disease (AD), will also increase. Therefore an early and accurate diagnosis of dementia is needed. Neuroimaging methods, such as positron emission tomography (PET), and single photon emission computed tomography (SPECT) are of great value, as are neurologic and neuropsychologic examinations, for studying and examining AD patients. Functional neuroimaging with PET, which is still used mainly for research, has demonstrated the presence of bilateral temporoparietal hypometabolism or hypoperfusion in AD patients.[1–3]

Although fluorine 18-labeled fluoro-2-deoxy-D-glucose (FDG) PET is widely used for a diagnosis in oncology, it is also a valuable clinical tool for diagnosing dementia.

Dementia can be classified into several diseases, each with a poor curability that is a neurodegenerative disease, one of which is AD, and curative or preventive disease: non-neurodegenerative disease (Table 1). FDG PET can be used as a diagnostic tool for these neurodegenerative diseases.

Here I would like to describe features of clinical PET for dementia, mainly of FDG-PET for AD.

Analyses of stereotactically normalized images using a statistical method

New methods for analyzing images have recently been developed. Statistical parametric mapping (SPM) 99 and

Received November 11, 2002, revision accepted November 11, 2002.

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Table 1 Classification of dementia

degenerative disease
Alzheimer's disease (AD)
dementia with Lewy bodies (DLB)
frontotemporal lobar degeneration (FTLD)
frontotemporal dementia (FTD):
Pick-type
frontal lobe degeneration type
motor neuron disease type
semantic dementia
progressive non-fluent aphasia
corticobasal degeneration (CBD)
progressive supranuclear palsy (PSP)
Huntington disease
spinocerebellar degeneration (SCD)
dentatorubural-pallidoluysian atrophy (DRPLA)
diffuse neurofibrillary tangle with calcification (DNTC)
Parkinson disease with dementia
cerebrovascular disease: vascular dementia (VaD)
cerebral infarction, cerebral hemorrhage, Binswanger disease
normal pressure hydrocephalus (NPH)
prion disease
Creutzfeldt-Jacob disease
infectious disease
progressive paralysis, herpes encephalitis, progressive multifocal encephalopathy, AIDS encephalopathy, Whipple disease
endocrine disorders
hypothyroidism, hypoparathyroidism, hypoadrenocorticism, hypopituitarism, syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
electrolytic imbalance
hyponatremia, hypernatremia
metabolic disease
vitamin B_1 deficiency, vitamin B_{12} deficiency, folic acid deficiency, hepatic encephalopathy, hypoxic encephalopathy
intoxication
alcoholic intoxication, Wernicke-Korsakoff syndrome, metal poisoning, organic compound poisoning, carbon monoxide poisoning
inborn error of metabolism
Wilson disease, Mitochondrial encephalopathy, leukodystrophy
neoplasm
brain tumor, intravascular lymphoma, etc.
collagen disease, inflammation
systemic lupus erythematosus, Sjögren's syndrome, neuro-Behçet syndrome, angiitis
demyelinating disease
multiple sclerosis
drug induced
trauma
cerebral contusion, chronic subdural hematoma
disuse syndrome

three-dimensional stereotactic surface projection (3D-SSP) have been widely used in research studies and as supplementary aids for clinical diagnosis.

3D-SSP was developed by Minoshima et al. for research studies and also for clinical diagnosis,[4] while SPM was developed for research use especially in activation studies.[5]

The concepts of these two methods are similar. In both methods, an individual brain is stereotactically normalized to a standard brain and analyzed pixel by pixel or voxel by voxel. This technique avoids subjectivity, the bias of observers, and the bias caused by underlying anatomic variations. The methods have good reproducibility, and are suitable for visual inspection with statistical maps (Fig. 1). 3D-SSP was found to be more suitable than SPM99 in anatomical standardization of atrophied brains[6] (Fig. 2). Some reports have found that these methods provide a better clinical diagnosis of AD than does conventional visual inspection diagnosis.[7,8]

Alzheimer's disease (AD)

Among degenerative dementias, AD is the most common. Characteristically, the disease starts with impairment of memory, followed by multiple domains of cognitive dysfunction. It is very important to differentiate AD from other demented state. Many studies have examined AD with PET. Here I describe how PET can be used for the clinical diagnosis of AD.

Cerebral association cortices

Metabolic and perfusional reductions have been clearly identified in the parieto-temporal association cortices with PET and SPECT[1–3] and are routinely used for the clinical diagnosis of AD. In the parieto-temporal association cortices of AD patients, the reduction in glucose metabolism is greater than the reductions in blood flow and oxygen metabolism.[3] Therefore FDG-PET, which shows cerebral glucose metabolism, is more useful than SPECT or PET measuring cerebral perfusion for the diagnosis of AD. As the demented state progresses, the area showing reduced metabolism or perfusion spreads into the frontal association cortices. Glucose metabolism in the posterior cingulate and precuneus is affected starting at the early stage of AD[9,10] as shown by surface rendered MR imaging (Fig. 3), FDG-PET imaging (Fig. 4), and 3D-SSP imaging (Fig. 5).

Medial temporal cortices

The magnitude of the reduction in perfusion or glucose metabolism in the hippocampus is not as large as that in the cortices.[11,12] Similar results were obtained with SPM and 3D-SSP analyses of mild and moderate AD patients.[12] This was unexpected in view of previous results that showed atrophy and clinical dysfunction in the hippocampus of AD patients, and suggests that the pathophysiology of the hippocampus in AD is more complex than was previously thought.

Relatively preserved metabolic area in AD

In AD patients, cerebral blood flow and glucose metabo-

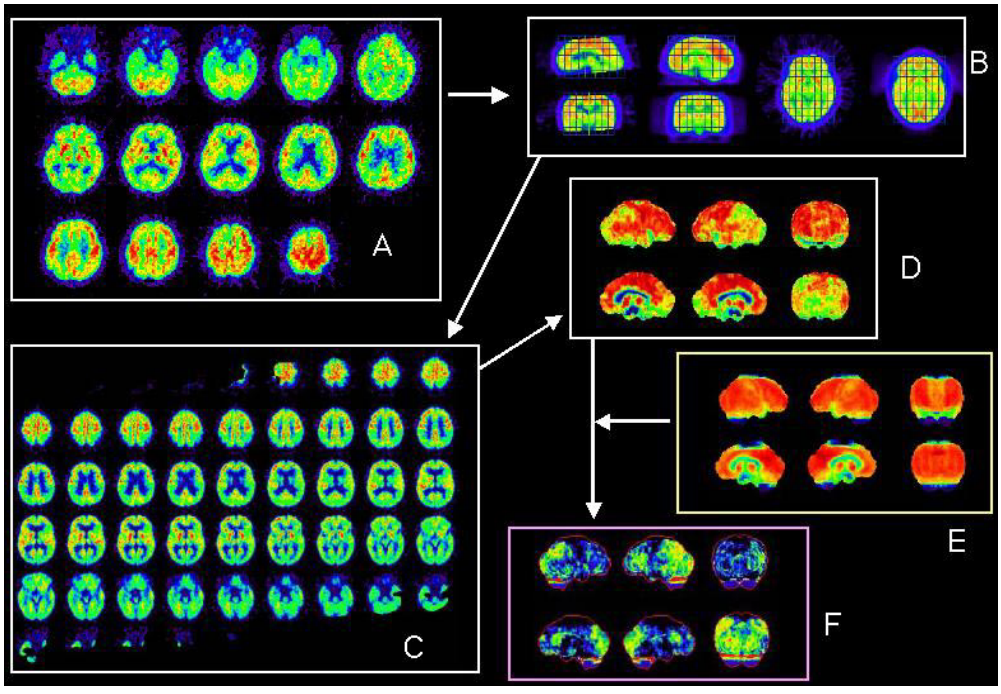

Fig. 1 Process of 3D-SSP. A: original FDG-PET image of a patient with DLB. B: matching of the original image of the patient with DLB to a template image. C: anatomically standardized image of the patient with DLB. D: 3D-SSP image of the FDG-PET image of the patient with DLB. E: 3D-SSP image of the averaged FDG-PET image of 20 normal volunteers. F: Z-score map of the patient with DLB.

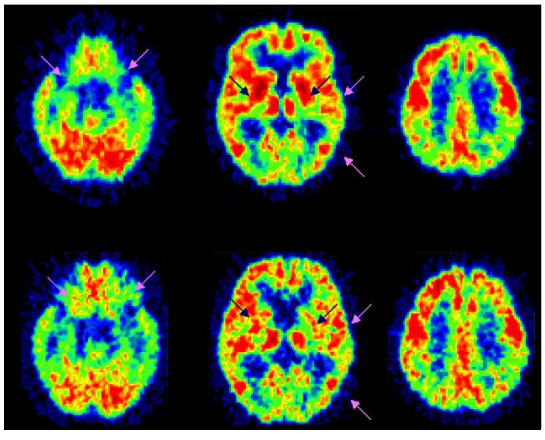

Fig. 2 Difference between the standardized images of 3D-SSP and SPM. There are some slight differences between the two images after anatomical standardization by 3D-SSP and SPM methods. Black arrows show different shape of the striatum and pink arrows show different contour of the gyri and lobes between the two methods. (*Upper row:* after standardization by 3D-SSP, *Lower row:* after standardization by SPM)

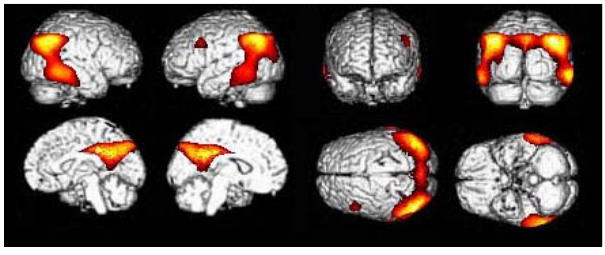

Fig. 3 Typical metabolic decreased areas in AD. The parieto-temporal, posterior cingulate and precuneus areas have regions with significantly reduced glucose metabolism compared with normal controls. These areas are clearly shown by surface rendered MR images.

lism are relatively preserved in the primary sensorimotor cortices, primary visual cortices, basal gangli, thalami, cerebellum, and the pons.[13–15] These areas can be used for a reference region for normalization of the absolute values of these quantities in each individual. However the glucose metabolism in these areas in patients with severe AD is significantly lower than that in normal controls. The cerebellar glucose metabolism in groups of patients with mild and moderate AD groups is also lower than that in normal controls, but the differences are not significant. It is important to note that even in the occipital cortices in AD patients, the glucose metabolic value was lower in AD patients than that in normal controls. Kumar et al.[16] reported that glucose metabolism in the primary sensorimotor regions was even lower in mild AD patient than in normal controls. The glucose metabolic rate in the primary sensorimotor regions in AD patients in our previous study also tended to be lower than that in the control

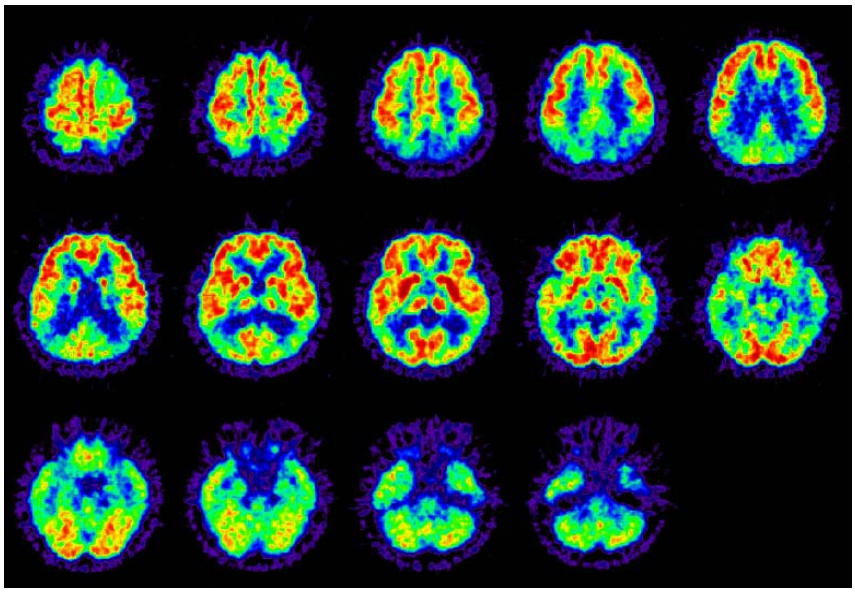

Fig. 4 Typical FDG-PET image of a patient with AD. This case is a 52-year-old female whose MMSE score was 19. Typical AD reduction pattern is shown on the axial plane images.

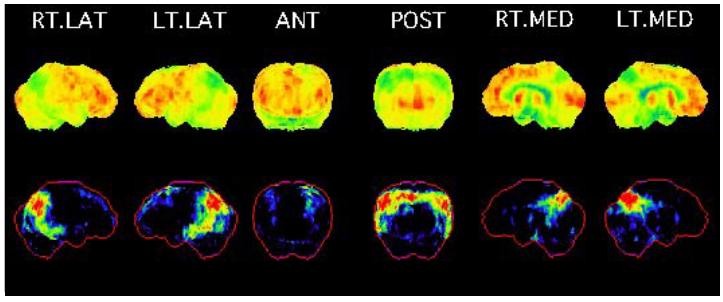

Fig. 5 3D-SSP image of a patient with AD. 3D-SSP image of the same patient in Figure 4. Bilateral parieto-temporal and posterior cingulate glucose metabolic reduction is well demonstrated.

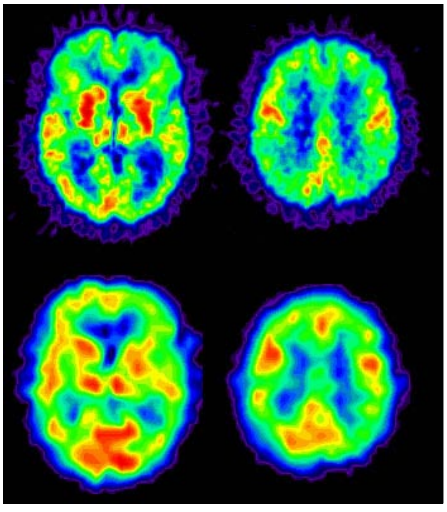

Fig. 6 FDG-PET (*upper row*) and IMP-SPECT image (*lower row*) of a patient with DLB. This is a 68-year-old female who complained of fluctuating cognitive functions, recurrent visual hallucinations. MMSE score was 19. Both PET and SPECT images show diffuse metabolic or blood flow decrease in the whole brain excluding the primary sensorimotor area, basal ganglia and thalamus. This disease is characterized by decreased occipital metabolism on the PET image. However, the SPECT image does not clearly demonstrate a decrease in occipital blood flow.

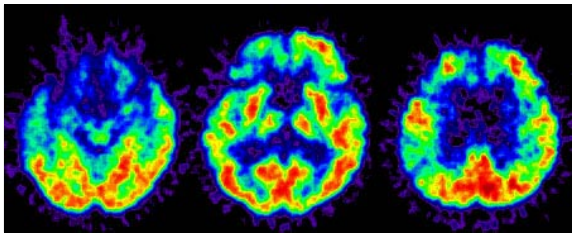

Fig. 7 Typical FDG-PET image of a patient with FTD. This case is a 62-year-old female whose MMSE score was 25.

group.[17] All the regions are connected with each other, and global neurodegeneration and remote effects from severely affected areas contribute to the reduction of whole brain glucose metabolism. Regional metabolic data that is normalized with respect to the values in these areas may err in severe AD patients.

Different pattern of metabolic impairment between early and late onset type of AD

There are significantly different patterns of metabolic impairment between early onset (EO) and late onset (LO) AD patients.[18–20] In EO AD patients, glucose metabolism is severely affected in the parietal and posterior cingulate

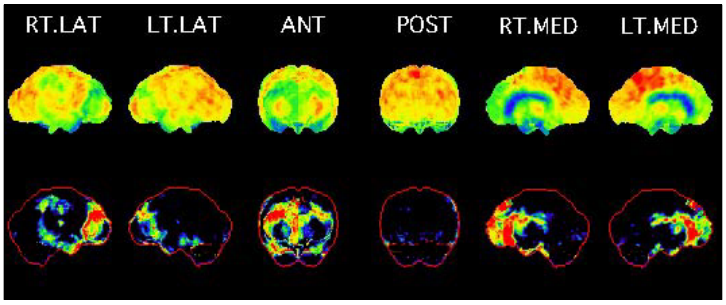

Fig. 8 3D-SSP image of a patient with FTD. 3D-SSP image of the same patient in Figure 7. Bilateral frontotemporal glucose metabolic reduction is well demonstrated.

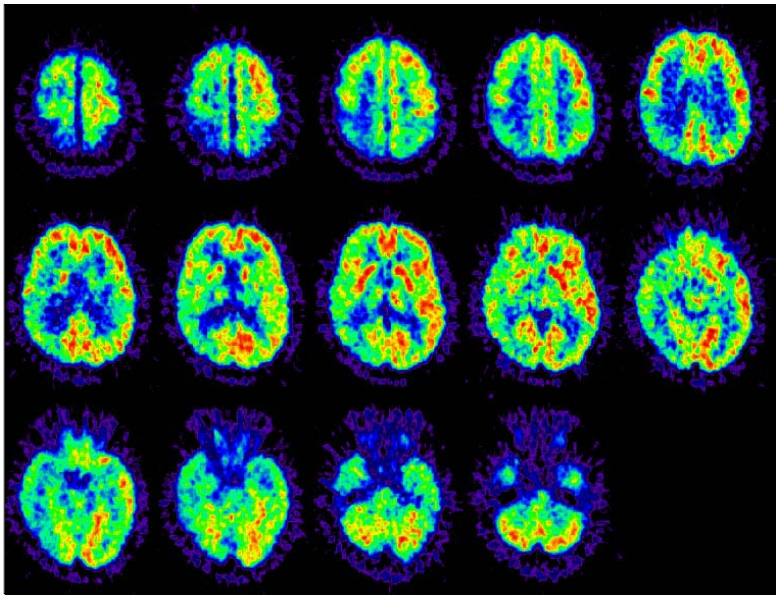

Fig. 9 Typical FDG-PET image of a patient with CBD. This case is a 62-year-old female whose MMSE score was 25.

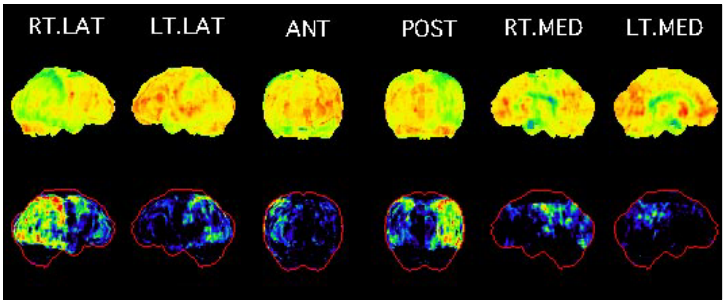

Fig. 10 3D-SSP image of a patient with CBD. 3D-SSP image of the same patient of Figure 9. Right parietotemporal glucose metabolic reduction is well demonstrated.

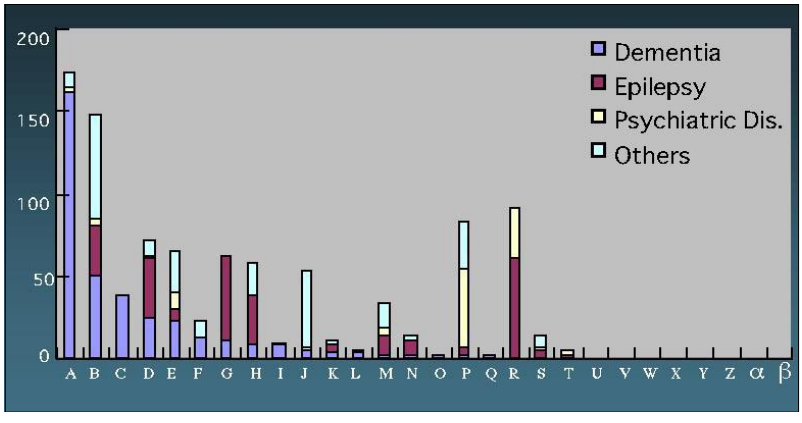

Fig. 11 Numbers of cases of various diseases at the 28 PET centers. Center A is my institute which is dedicated to dementia and cognitive disorders.

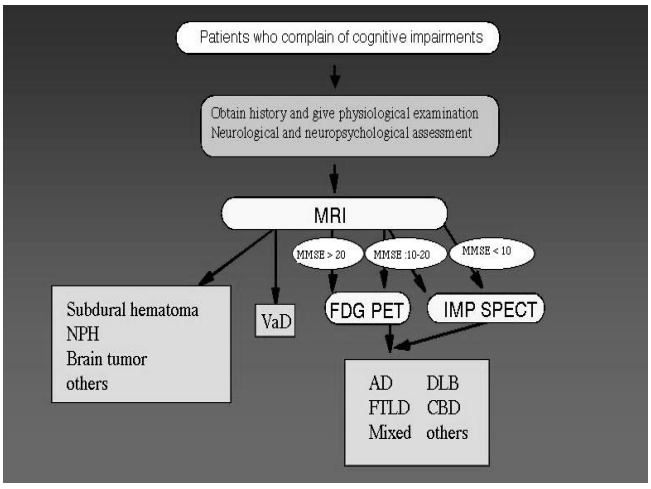

Fig. 12 Decision tree for diagnosis of dementia at Hyogo Institute for Aging Brain and Cognitive Dementia. At my institute, mild and moderate dementias are examined with PET and severe dementia is subjected to a SPECT examination but not to a PET examination.

cortices, while in LO AD patients it is severely affected in the limbic system and medial frontal lobe, though these regions may experience not only a metabolic decline but also a partial volume effect due to atrophy. This provides biological evidence for the observed difference in regional cerebral glucose metabolism between EO and LO AD patients and explains the different clinical symptoms between EO and LO AD patients. This phenomenon makes it difficult to distinguish LO AD patients at the early stage from aged normal people with age-matched memory impairment.

Genotype of glucose metabolism in AD

Apolipoprotein E (APOE) is well-known as a genetic risk factor for AD. Especially APOE $\varepsilon 4$ allele is the major factor which increase the onset of AD in the aged people. Premorbid nondemented subjects who have an APOE $\varepsilon 4$ allele have been found to have reduced glucose metabolism in the parietotemporal association cortices and posterior cingulate gyri.[21,22] However, after the onset of AD, the patterns of glucose metabolism do not differ between patients with or without the APOE genotype.[23,24]

Therapy monitoring

To obtain transient cognitive and behavioral stabilization of patients with AD, long-term therapy with the acetylcholinesterase inhibitor donepezil has been shown to stabilize cognitive function and the behavior of AD patients. The effect of donepezil in a patient can be monitored or predicted with functional imaging. FDG-PET has not yet been used for this purpose, although SPECT has been used by some studies.

In a PET study, [^{11}C]CP-126,998, an *N*-benzylpiperidinebenzisoxazole, was used to image brain acetylcholinesterase (AChE) distribution in healthy controls before and after administration of donepezil.[25] This study indicated that PET imaging may be useful for quantifying the distribution of AChE in the brain and may be useful for the diagnosis and treatment of patients with disorders of cholinergic neurotransmission. AChE activities in the brain of patients with AD were measured once before and once during donepezil treatment using PET and *N*-[^{11}C]methylpiperidin-4-yl acetate, and showed that inhibition of AChE by donepezil treatment improved cholinergic activity in the brain.[26] After donepezil treatment, cerebral cortical inhibition of AChE in AD brains averaged only 27%. This showed that clinical trials of donepezil are not testing the effect of nearly complete cerebral cortical inhibition of AChE.[27]

Cerebral blood flow (CBF)

About ten years ago, cerebral blood flow (CBF) imaging with O-15 water PET was not thought to be useful for clinical diagnosis of AD.[28] This was due to the low spatial resolution of PET scanners. Since then the performance of PET scanners has greatly improved and CBF images produced with O-15 water and PET have been close metabolic images made with FDG-PET. The regions of reduced CBF in AD are the same as the regions of reduced glucose metabolism in AD. Both perfusion and glucose metabolism are reduced in the posterior cingulate gyrus of AD patients. Perfusion in the posterior cingulate gyrus is considered to be decreased in patients with mild AD,[29] reflecting the pathological changes and metabolic reduction that have been previously observed in this region in mild AD patients. Thus CBF images are very useful for the diagnosis of AD.[8]

Mild cognitive impairment (MCI)

Mild cognitive impairment (MCI), which is considered to be a transitional stage between aging and AD, is becoming an increasingly important topic of study in the field of aging and dementia. However, MCI is a heterogeneous clinical syndrome for which no international diagnostic criteria have yet been established. If FDG PET demonstrates a glucose reduction pattern in MCI patients that is the same as the glucose reduction pattern in AD patients, then it is likely that the patient will show symptoms of AD in the near future.

Dementia with Lewy bodies (DLB)

Dementia with Lewy bodies (DLB) has been recognized as a clinical entity of primary degenerative dementia that is pathologically characterized by the presence of Lewy bodies in cortical, subcortical, and brainstem structures. In 1996, an international workshop recommended DLB as a generic term, and proposed criteria for clinical and pathological diagnoses.[30] By using FDG-PET, regional glucose metabolism in the occipital association cortex and primary visual area was shown in 6 patients with

autopsy-proven DLB.[31] The relative hypometabolism was more severe in the occipital cortices and less severe in the medial temporal lobes in patients with clinical diagnosis of Parkinson's disease and dementia, some of whom would be presumably classified as DLB, than in patients with AD.[32] The involvement of the medial and lateral occipital lobes is uniquely observed in patients with DLB. Patients with DLB, like patients with AD, show little glucose metabolism change in the sensorimotor cortex, basal ganglia, thalamus, and pons.[33,34] Occipital hypometabolism is the feature of DLB that discriminates it from AD (Fig. 6). Pathologically the occipital cortices are not so involved in DLB patients, though the occipital glucose metabolism is reduced. One reason for this may be that the dopaminergic system is affected in DLB patients.[31,32] Another reason is that the activity of a cholinergic enzyme, choline acetyltransferase, in the temporo-parietal and occipital neocortex is reportedly lower in DLB than in AD[35,36] and that neurodegenerative processes in the basal nucleus of Meynert may preferentially involve the cholinergic neurons projecting to the occipital lobe, and cause occipital dysfunction.

Frontotemporal lobar degeneration (FTLD)

Frontotemporal dementia (FTD) is a comprehensive clinical entity of primary degenerative dementia that is characterized by peculiar behavioral changes arising from frontotemporal involvement. The Lund/Manchester groups proposed clinical and pathological criteria for FTD in 1994.[37] According to these criteria, three types of histologic change (Pick-type, frontal lobe degeneration type, and motor neuron disease type), underlie the atrophy and share an anatomical distribution in the frontal and temporal lobes. Recently, frontotemporal lobar degeneration (FTLD), which includes semantic dementia and progressive non-fluent aphasia and FTD, has been used to classify patients with frontal and temporal symptoms.[38] (Table 1).

Despite its being named after the frontotemporal region, FTD has a more widespread hemispheric metabolic derangement. The medial temporal region and the subcortical structures including the basal ganglia and thalamus are affected. Reduced glucose metabolism in several regions (the orbital gyrus, anterior cingulate gyrus, frontal cortices, anterior temporal cortices, hippocampus, and subcortical structures) are consistent with the pathological features of FTD. Although the cortical involvement is accentuated in the frontal lobes and anterior temporal lobes, the involvement of the parietal region is also noted by FDG PET (Figs. 7, 8) and parietal pathological involvement has been recognized in post-mortem studies of patients with advanced FTD. Moreover, glucose metabolism in the sensorimotor cortex and the cerebellar cortex can be also decreased in FTD.[39]

Corticobasal degeneration (CBD)

Corticobasal degeneration (CBD) is a slowly progressive disorder characterized by akineto-rigid syndrome, dystonia, myoclonus, apraxia, alien limb syndrome, and cortical sensory loss, which occur with asymmetric onset.[40] The pathological hallmark is corticodentatonigral degeneration with neuronal achromasia. Cortical lesions predominate in the fronto-parietal cortex, whereas the medial temporal structures are relatively spared. Subcortical regions including the substantia nigra, thalamus, globus pallidus, claustrum, subthalamic nucleus, red nucleus, striatum, and midbrain tegmentum are also involved to varying degrees. CBD patients frequently have cognitive deficits and substantial dementia, as well as extrapyramidal motor symptoms, that are distinctive from those of patients with other degenerative dementing illnesses. Several studies have shown hypoperfusion or hypometabolism in the frontal, central and parietal cortices and in the subcortical structures including the thalamus, caudate nucleus, and putamen, with marked asymmetry between the two hemispheres.[41–43]

The CBD patients with symptoms of dementia show greater glucose metabolic asymmetries in the lateral frontal, lateral temporal, central, and lateral parietooccipital regions than did the normal controls (Figs. 9, 10). Metabolic asymmetries in the pre- and post-central gyri, and thalamus were greater in the CBD patients than in the AD patients. Metabolic asymmetries in the pre- and post-central gyri and basal gangli are a distinctive feature of CBD.[44]

The most striking pathologic changes in CBD reportedly appear in the pre- and post-central gyri and parietal association cortices. PET studies clearly indicate that metabolic deficits in the primary sensorimotor cortices and superior parietal lobules are the most striking features of CBD. Decreases in absolute glucose metabolism are also observed in several regions of the brain in CBD.[44]

Progressive supranuclear palsy (PSP)

Progressive supranuclear palsy (PSP) is a neurodegenerative disorder of middle and late age presenting with dementia and parkinsonism. The neurological features of PSP included impaired ocular motility, pseudobulbar palsy, and axial dystonia. In PSP patients, the basal ganglia and brain stem are the main loci of pathological changes, while the cortical regions have only a slight pathological involvement. In patients with PSP, glucose metabolism is decreased in the lateral and medial frontal lobes, caudate nucleus, and midbrain as compared with age-matched healthy controls.[45,46] This may be due to the fact that the frontal lobe, as a central constituent of the fronto-subcortical network, is closely connected with subcortical structures. Behavioral derangement and cognitive deficits which are characteristic of PSP and which epitomize subcortical dementia, such as disinhibited and stereotyped behaviors, apathy, mental slowness, and

attentional and executive dysfunctions, are likely due to frontal hypofunction, and FDG-PET demonstrates well these pathophysiological situations.

Creutzfeldt-Jacob disease (CJD)

Creutzfeldt-Jacob disease (CJD) is thought to be an infectious prion disease. There have been no comprehensive PET or SPECT studies of CJD. Various reduced metabolic and perfusional patterns in patients with CJD have been reported.[47–49] Henkel et al.[50] reported that their CJD patients had a reduction of cerebral glucose metabolism in at least one temporal or parietal region. In addition, in 7 of their 8 CJD cases and in 3 of 4 CJD cases from the literature, the occipital lobe, the cerebellum or the basal ganglia were involved. However, the pattern of reduced glucose metabolism in CJD is similar to that in AD, especially at the very early stage, so it is very difficult to diagnose CJD only by functional imaging. Diffusion weighted imaging with MRI has been shown to be useful for diagnosing Creutzfeldt-Jacob disease.[51]

Wernicke-Korsakoff syndrome

Wernicke-Korsakoff syndrome (WKS) is a neurobehavioral disorder that consists of severe amnesia, disorientation, and confabulation, but with preserved intelligence. In chronic alcoholism, FDG-PET showed reduced glucose metabolism in the medial frontal area.[52] Decreased glucose metabolism in the basal cortex, cingulate gyrus, hippocampus and thalamus in patients with WKS have been reported.[53,54] The decreased perfusion and metabolism in the fronto-temporal area might be a remote effect of the dysfunction of the Papez circuit.

Normal pressure hydrocephalus (NPH)

Normal pressure hydrocephalus (NPH) is characterized by globally diminished glucose metabolism,[55] although it has no distinct pattern. The absence of a distinct pattern may be due to a non-specific association between NPH syndrome and different degenerative disorders. The metabolic heterogeneity, together with the heterogeneous histopathological findings, indicate the necessity of re-evaluating the pathogenesis of the NPH syndrome. These heterogeneities may account for the high variability in the success rate of shunt surgery.[56]

Vascular dementia (VaD)

Vascular dementia (VaD) can be easily diagnosed from clinical symptoms and using MRI or X-ray CT. A PET study is not needed for patients with pure VaD. However, VaD is sometimes associated with AD pathology, and so VaD patients should be examined with FDG PET to determine whether they have an AD metabolic reduction pattern.

Clinical application of FDG PET to dementia in Japan

In Japan in 2001, 36 PET centers and 48 PET scanners were in operation. In April, 2002, Japanese health insurance began covering the use of FDG PET for various diseases such as cancers, epilepsy, and brain tumors, but FDG PET is not yet approved for dementia.

Table 2 Numbers of FDG PET examinations given at HIMABCD in 2001 for various diseases

Alzheimer disease (AD)	100
Dementia with Lewy bodies (DLB)	15
Frontotemporal lobar degeneration (FTLD)	4
Corticobasal degeneration (CBD)	2
Progressive supranuclear palsy (PSP)	3
Depression	3
VaD	2
Others	7
possible AD	17
possible DLB	5
possible FTD	9
possible CBD	2
possible PSP	2
Normal volunteers	24
Total	195

All Japanese PET centers are required to have their own cyclotrons. Government regulations prohibit PET centers from having satellite facilities or from supplying FDG to other institutes, even though such operations may be more efficient.

In April 2002, I sent questionnaires to 36 Japanese PET centers to determine how many cases of various diseases (dementia, epilepsy, psychiatric disease, and other brain diseases excluding ischemic diseases) they examined with FDG PET in 2001.

Twenty-eight centers responded. The results are shown in Figure 11. The highest number of dementia cases was examined at my institute (Center A), which is dedicated to dementia and cognitive impairments. Each of the other centers examined less than 50 cases of dementia. Nine centers did not examine any cases of dementia and five centers did not examine any brain diseases. The latter centers are dedicated to cancers or medical check ups.

Figure 12 shows a decision tree for diagnosing dementia at my institute.

Patients who complain of cognitive impairments are examined by neurologists or psychiatrists to obtain their history, given physiological examinations, and subjected neurological and neuropsychological assessments.

Next, MRI images of the brain are obtained in order to exclude several pathologies (subdural hematoma, normal pressure hydrocephalus, brain tumors and vascular dementia). The cases that are suspected of having AD or other degenerative disorders are examined by FDG PET or IMP SPECT. FDG PET is used only for patients with mild or moderate cognitive impairment (corresponding to a mean Mini-Mental State Examination Score of 21.4 ± 4.9), i.e., it is never used for severely demented cases. AD is finally diagnosed if FDG PET shows the metabolic

reduction pattern of AD. Our institute examined 171 cases of various diseases in 2001 (Table 2) with generally satisfactory results. FDG PET has an ability to differentiate these diseases. Of these 171 patients, 35 (20%) patients, who were at very early stage of memory impairment or cognitive disorders, could not be diagnosed, even with FDG PET. These subjects should be carefully followed up.

Acknowledgments

Below are the Japanese PET centers which replied to my questionnaires. I thank them for their cooperation.

Akita Research Institute of Brain and Blood Vessels; Chiba University; Chubu Ryogo Center, Kizawa Memorial Hospital; Fukui Medical University; HIMEDIC Imaging Center at Lake Yamanaka; Hyogo Institute for Aging Brain and Cognitive Disorders; Institute of Biomedical Research and Innovation; International Medical Center of Japan; Kanazawa Cardiovascular Hospital; Kyushu University; Mie University; Nagoya City Rehabilitation Center; Nagoya Diagnostic Clinic; National Cancer Center Hospital East; National Cardiovascular Center; National Center Hospital for Mental, Nervous, and Muscular Disorders, National Center of Neurology and Psychiatry; National Institute for Longevity Sciences, National Chubu Hospital; Nikko Memorial Hospital; Osaka University Hospital; Osaka City University; Positron Medical Center, Hamamatsu Medical Center; Positron Medical Center, Tokyo Metropolitan Institute of Gerontology; Shiga Medical Center; Tohoku University; University of Tokyo; Yokohama City University; Yokohama Stroke and Brain Center.

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