PET Approaches for Diagnosis of Dementia

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The number of patients with dementia is progressively increasing worldwide. Dementia is a clinical diagnosis based on significant and persistent deficits of intellectual function, usually memory. Diagnostic imaging techniques for morphologic examinations (e.g., CT and MR imaging) and for functional examinations (e.g., SPECT and PET) are now used widely for supporting the diagnosis of dementia. Such imaging techniques can indicate the likely underlying pathology in a patient who meets the clinical criteria for dementia. In particular, amyloid imaging PET has been reported to show the pathophysiologic states of dementia. The PET radiopharmaceutical \([18\text{F}]\text{fluorodeoxyglucose}\) can detect regional glucose metabolism in patients with dementia and is the most widely available and useful biomarker for dementia diagnosis. However, to exclude several pathologies such as subdural hematoma, vascular dementia, normal pressure hydrocephalus, and brain tumors, clinical examination is first performed by using MR imaging because FDG-PET alone cannot detect these diseases. After this process, FDG-PET is then performed to detect early neurodegenerative dementia, differentiate neurodegenerative dementias, or suggest comorbidity of other neurodegenerative diseases. Herein, I review the various imaging approaches for dementia, with a particular focus on PET and new techniques or tracers.

**Alzheimer Disease**

Alzheimer disease (AD) is the most common dementia, which starts with impairment of memory followed by multiple domains of cognitive dysfunction. The 2011 criteria for AD\(^2,3\) was revised from that in 1984,\(^4\) and the recommendations regarding the respective roles of FDG-PET and MR imaging in AD and mild cognitive impairment (MCI) are conflicting. However, PET plays an important role as a biomarker in AD, as well as for functional and molecular imaging. For example, FDG-PET is described as a “neuronal injury” biomarker in AD.\(^2,3\)

**FDG-PET in Alzheimer Disease**

FDG-PET can demonstrate a glucose metabolic reduction in the parietotemporal association cortices, posterior cingulate, and precuneus regions at the early stage of AD (Fig 1). By contrast, in the healthy elderly brain, posterior cingulate glucose metabolism is much higher than that in other cortices, while parietal glucose metabolism is the same as that in the primary sensorimotor cortices (Fig 2). In the moderate-to-severe stages of AD, hypometabolic regions spread to the frontal association cortices, while metabolism in the striatum, thalamus, primary sensorimotor cortices, visual cortices, and cerebellum are relatively preserved despite disease progression. Because the magnitude of glucose metabolic reduction in the medial temporal lobe, including the hippocampus, is not as large...
as that in the parietotemporal or posterior cingulate cortices, a decrease in hippocampal glucose metabolism with progression from mild-to-moderate-stage AD is not usually demonstrated,5 despite obvious hippocampal atrophy at the early stage. Hippocampal glucose metabolism is somewhat decreased at the early stage of AD. However, it is difficult to detect the small reduction of hippocampal glucose metabolism in patients with early AD because the hippocampal glucose metabolism is smaller than the neocortical glucose metabolism, even in healthy subjects, and the magnitude of the decrease is modest. Thus, a method for detecting hippocampal metabolic reduction at an early stage of AD is required.6-8 However, Karow et al9 reported that FDG-PET has the same sensitivity as MR imaging for detecting brain degeneration in preclinical and mild AD, suggesting that MR imaging may be a more practical clinical biomarker for early detection of AD.

Mild Cognitive Impairment Due to Alzheimer Disease
Mild cognitive impairment consists of a heterogeneous pathology, and MCI due to AD is a transitional stage between aging and AD. MCI due to AD demonstrates the same glucose-reduction pattern as early AD (Fig 3), which predicts that the patient will show symptoms of AD in the near future. At the early stage of AD or MCI due to AD, it is difficult to detect the characteristic hypometabolic patterns on FDG-PET images by visual inspection. As such, statistical images are helpful. Nevertheless, FDG-PET generally has a higher accuracy than MR imaging for diagnosing early AD10,11 and for predicting rapid conversion of MCI to early AD.12 A combination of PET and other biomarkers is important because imaging and CSF biomarkers can improve prediction of conversion from MCI to AD.
compared with baseline clinical testing. FDG-PET appears to add the greatest prognostic information.13-16

**Effects of APOE on FDG-PET and Amyloid Imaging of Alzheimer Disease**

The apolipoprotein E gene (APOE) is a risk factor for late-onset AD, while the APOE e4 allele (e4) increases the risk and decreases the average age of dementia onset. Patients with early-onset AD who were APOE e4-positive showed a significant decrease in glucose metabolism in the medial temporal lobe compared with patients with APOE e4-negative AD.17 By contrast, in the late-onset group, there were no differences in the glucose-metabolic reduction patterns between patients with APOE e4-positive and -negative AD. A similar pattern of cerebral hypometabolism was also detected between patients with APOE e4-positive and -negative AD but with stronger abnormalities in e4 carriers in the parietal, temporal, and posterior cingulate cortical regions.18 Recently Ossenkoppele et al19 found a reversed APOE e4 dose effect for amyloid deposition in the frontal lobe, whereas APOE e4 carriership was associated with more profound metabolic impairment in the posterior parts of the cortex. These findings suggest that the APOE genotype has a differential effect on the distribution of amyloid plaques and glucose metabolism.

**Statistical Voxel-Based Analysis Approach for Alzheimer Disease Diagnosis**

Minoshima et al20,21 first developed the 3D stereotactic surface projection system (3D-SSP; http://www.rad.washington.edu/research/Research/groups/nbl/neurostat-3d-ssp) and used z score images to aid visual inspection of individual FDG images for diagnosing AD (Fig 4). The Statistical Parametric Mapping program (Wellcome Department of Imaging Neuroscience, London, UK) was developed as a tool for analysis of PET and functional MR imaging images. For automatic diagnosis, Herholz et al22 proposed the t-sum method of calculating the total t-values in a region-of-interest template by using the Statistical Parametric Mapping program; by using this method, the parietotemporal and frontal regions were found to be AD-specific compared with healthy elderly subjects. An automatic diagnosis system by using 3D-SSP and a region-of-interest template was proposed for discriminating those with early AD from healthy subjects.23,24 This system was also applied to distinguish patients with dementia with Lewy bodies (DLB) from those with AD.24 All these systems require a data base of healthy controls. More recently, however, a data base–independent system was proposed by using t-statistics between parietal and sensorimotor glucose metabolism in individual subjects.25 Mevel et al26 proposed an automatic system for determining hippocampal metabolism by using a voxel-based method and partial volume correction, which was useful in detecting MCI.

**Combination of MR Imaging and PET**

Most of the studies described above have focused on only a single technique such as structural MR imaging or PET. Yuan et al12 performed a meta-analysis and meta-regression on the diagnostic performance data for MR imaging, SPECT, and FDG-PET in subjects with MCI and reported that FDG-PET performed slightly better than SPECT and structural MR imaging in the prediction of conversion to AD in patients with MCI, while a combination of PET and structural MR imaging improved the diagnostic accuracy of dementia. Kawachi et al10 also compared the diagnostic performance of FDG-PET and voxel-based morphometry (VBM) on MR imaging in the same group of patients with very mild AD and reported an accuracy of 89% for FDG-PET diagnosis and 83% for VBM–MR imaging diagnosis, while the accuracy of combination FDG-PET and VBM-MR imaging diagnosis was 94%. These studies suggest that a combination of imaging modalities may improve the diagnosis of AD.

**Amyloid Imaging in Alzheimer Disease**

The most widely used tracer for amyloid imaging is 11C-Pittsburgh compound-B (PiB),27 which has a high affinity to amyloid β peptide (Aβ) aggregates. The 11C-BF 227 ligand is also used for amyloid imaging,28 though its uptake contrast between amyloid-positive and -negative brain tissue is not as high as that for PiB, and it is used only at a few institutions in Japan. Because the
half-life of the $^{11}$C isotope is short, $^{11}$C-PiB is available only in specific institutions that have a cyclotron and a synthesis system. Conversely, the half-life of the $^{18}$F isotope is 110 minutes, and $^{18}$F-labeled amyloid imaging tracers will become widely used following production by radiopharmaceutical companies. Currently there are a few $^{18}$F-labeled amyloid imaging tracers available (Table 1), though in 2012, $^{18}$F-AV-45 (florbetapir) was approved by the FDA for PET imaging of $\beta$-amyloid neuritic plaques in the living brain. $^{18}$F-AZD4694 is also expected to be a good radioligand for both diagnostic use and evaluation of disease-modifying therapies in AD. 

Amyloid PET is helpful in the diagnosis of AD. However, the timing of amyloid accumulation is at a preclinical stage of AD. Early $\beta\beta$ accumulation and increased vulnerability to $\beta\beta$ pathology play critical roles in the pathogenesis of patients with early-onset AD. $\beta\beta$ deposition initiates the pathologic cascade but is not the direct cause of cognitive impairment, and intermediate $\beta\beta$ deposit may represent individuals with AD coexistent with other pathologies. Furthermore, amyloid deposit is not unique to AD and can be found in other diseases or healthy elderly people.

At present, amyloid PET is not indicated in patients with preclinical AD or healthy subjects, except for clinical trials or research studies. The appropriate usage criteria for amyloid PET were proposed by the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer’s Association. These criteria indicate that appropriate use of amyloid PET includes the following: 1) patients with persistent or progressive unexplained MCI; 2) patients with possible AD with unclear clinical presentation, either an atypical clinical course or an etiologically mixed presentation; and 3) patients with progressive dementia and atypically early age of onset. Inappropriate use of amyloid PET includes the following: 1) in patients with typical probable AD, 2) for determining the severity of dementia, 3) in subjects with a positive family history of dementia or the presence of $\text{APOE e4}$, 4) in patients with a cognitive problem that is unconfirmed on clinical examination, 5) as a replacement for genotyping for suspected autosomal mutation carriers, 6) in asymptomatic subjects, and 7) for nonmedical use (eg, legal, insurance coverage, or employment screening).

### Dementia with Lewy Bodies

Dementia with Lewy bodies is the second most common neurodegenerative dementia following AD and is characterized pathologically by the presence of Lewy bodies in cortical, subcortical, and brainstem structures. DLB belongs to the spectrum of Lewy body diseases including Parkinson disease (PD), where Lewy bodies remain in the brain stem. PD with dementia has the same pathology as DLB, though clinical symptoms slightly differ. Parkinsonism appears $>1$ year earlier than cognitive dysfunctions in PD with dementia. In 2005, the criteria for clinical and pathologic diagnoses were revised and included an important role for functional and morphologic imaging. For example, low dopamine transporter uptake in the basal ganglia on SPECT and PET imaging scans is regarded as a suggestive feature for DLB, while supportive features include relative preservation of medial temporal lobe structures on CT/MR imaging and generalized low uptake on SPECT/PET, with reduced occipital activity and abnormal (low) uptake on metadobenzylguanidine myocardial scintigraphy. Relative preservation of the hippocampus in DLB compared with prominent hippocampal atrophy in AD is also a common finding, though there are many overlapping areas of hippocampal atrophy between patients with DLB and those with AD, making it impossible to distinguish a patient with DLB from one with AD by using only a finding of hippocampal atrophy.

The hypometabolic regions in patients with DLB are similar to those in AD, though patients with DLB exhibit a difference in the involved occipital lobe (Fig 5). The relative metabolic reduction was more severe in the occipital cortices and less severe in the medial temporal lobes in DLB compared with AD, and occipital hypometabolism is a key feature of DLB that discriminates it from AD. 

### Table 1: Representative radiopharmaceuticals for amyloid imaging

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
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<tbody>
<tr>
<td>$^{11}$C-PiB</td>
<td>$^{11}$C-2-[4-(methylaminophenyl)-6-hydroxybenzothiazole] $^{32}$</td>
</tr>
<tr>
<td>$^{11}$C-BF27</td>
<td>$^{11}$C-2-[2-Dimethylaminothiazol-5-yl]ethenyl-6-[2-(fluoroethoxy)benzoazol] $^{28}$</td>
</tr>
<tr>
<td>$^{11}$C-AZD2184</td>
<td>N-[11$^C$]methy]-2-[6-methyl amino pyridine-3-yl]-benzod[\text{d}]thiazole $^{66}$</td>
</tr>
<tr>
<td>$^{18}$F-FDDNP</td>
<td>2-[1-6-[18$^F$]fluoroethyl]methylamino]-1-2-naphthy[ethyliden]malononitrile $^{67}$</td>
</tr>
<tr>
<td>$^{18}$F-PiB</td>
<td>2-[3-[18$^F$]fluoro-4-(methylaminophenyl)-l,3-benzothiazole $^{68}$</td>
</tr>
<tr>
<td>$^{18}$F-BAY94–972</td>
<td>4-(N-methylamino)-4’-[2-(2-[18$^F$]fluoroethoxy)ethoxy]-ethoxy)-stilbene $^{69}$</td>
</tr>
<tr>
<td>$^{18}$F-AZD4694</td>
<td>2-[2-[18$^F$]fluoro-6-(methylaminopyridin-3-yl)benzofuran-5-ol] $^{30}$</td>
</tr>
</tbody>
</table>

Note: $^{18}$F-AV45 indicates florbetapir; $^{18}$F-BAY94–972, florbetaben; $^{18}$F-PiB, flutemetamol.
Nevertheless, pathologically, the occipital cortices are not as involved in patients with DLB. These findings are also seen in patients with PD and PD with dementia because DLB and PD with dementia are in the same disease entity, involving spread of Lewy bodies in the cerebral cortices.

Dopamine transporter imaging with $^{123}$I-$N$-o-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ([$^{123}$I] FP-CIT) SPECT imaging is useful for diagnosing DLB and exhibits a diagnostic accuracy sufficient to distinguish DLB from AD. However, this imaging technique cannot distinguish other degenerative dementias with Parkinsonism (eg, progressive supranuclear palsy (PSP) and multiple system atrophy), while FDG-PET imaging can distinguish DLB from PSP and multiple-system atrophy. $^{123}$I-metaiodobenzylguanidine cardiac scintigraphy, which is typically used for myocardial innervation, also demonstrates a high sensitivity and specificity in patients with suspected DLB and provides an accurate examination for differential diagnosis between DLB and other dementias.

**Amyloid Imaging in Dementia with Lewy Bodies**
Shimada et al reported that amyloid deposits are associated with AD-like atrophy in patients with DLB/PD with dementia. Patients with DLB have higher amyloid deposits than patients with PD and PD with dementia. Amyloid deposits have been linked to cognitive impairment in DLB and may contribute to the timing of the onset of dementia relative to that of Parkinsonism in Lewy body dementia. However, as shown in Fig 6, severe metabolic reduction was seen in some patients with DLB despite no evidence of amyloid deposits. In particular, regional metabolic reduction in patients with DLB was observed in the parietotemporal, posterior cingulate, and frontal association cortices, which are the same regions affected in AD but are not correlated with amyloid deposit.

**Frontotemporal Lobe Degeneration**
Frontotemporal lobe degeneration (FTD) is a heterogeneous group of diseases involving frontal and/or anterior temporal lobe degeneration and associated dementia. Frontotemporal dementia is a comprehensive clinical entity of primary degenerative dementia characterized by peculiar behavioral changes and includes 3 types of histologic change (pick-type, frontal lobe degeneration type, and motor neuron disease type). Frontotemporal lobe degeneration includes FTD, semantic dementia, and progressive nonfluent aphasia, while FTD is now used clinically to classify patients with frontal and temporal symptoms.

In FTD, frontal and anterior temporal glucose metabolism is decreased, though the medial temporal region and the subcortical structures, including the striatum and thalamus, are also affected (Fig 7). According to a VBM study of FTD, metabolic and atrophic changes occur in the bilateral frontal and temporal lobes.
whereas the affected regions of metabolism are larger and more severe than those of atrophy in the frontal lobe. In patients with semantic dementia, asymmetrically severely decreased temporal metabolism can be demonstrated on FDG-PET images (Fig 8). These areas can spread to the frontal and parietal cortices, though the degree of metabolism alteration is not as marked as in the anterior temporal cortices.

**Amyloid Imaging in Frontotemporal Lobe Degeneration**
In a study of PiB retention in patients with FTD, Engler et al\(^52\) reported that most patients with FTD displayed no PiB retention and that PiB could potentially aid in differentiating FTD and AD. Rabinovici et al\(^51\) also reported that 8/12 patients with frontotemporal lobe degeneration had negative amyloid deposits, and the 4 PiB-positive patients with frontotemporal lobe degeneration may suggest the mimicking of AD pathology.

**Progressive Supranuclear Palsy**
Progressive supranuclear palsy is a neurotauopathic degenerative disorder presenting with Parkinsonism and dementia. The neurologic features include impaired ocular motility, pseudobulbar palsy, and axial dystonia. The basal ganglia and brain stem are the main loci of pathologic involvement. MR imaging studies demonstrate brain stem atrophy with a so-called “humming bird” sign, though these findings are not often seen at the early stage of PSP. However, FDG-PET demonstrates decreased glucose metabolism in the midbrain, the lateral and medial frontal lobes, and the caudate nucleus, even at the early stage of PSP (Fig 9)\(^52,53\) and can distinguish PSP from other diseases with Parkinsonism.\(^54,55\)

**Corticobasal Degeneration**
Corticobasal degeneration (CBD), which belongs to the corticobasal syndrome, is characterized by akineto-rigid syndrome, dystonia, myoclonus, apraxia, alien limb syndrome, and cortical sensory loss, and typically occurs with asymmetric onset. CBD is pathologically a tauopathic neurodegenerative disease and includes \(\tau\)-immunoreactive neuronal cytoplasmic inclusions, oligodendroglial inclusions, and astrocytic plaques. FDG-PET demonstrates hypometabolism in the frontal and parietal cortices and the subcortical structures, including the thalamus, caudate nucleus, and putamen, with marked asymmetry between the 2 hemispheres. Patients with CBD with symptoms of dementia show an AD-like metabolic reduction pattern but asymmetric glucose-metabolic reduction in the lateral frontal, lateral temporal, medial and lateral parietal cortices; the pre- and postcentral gyri; and the thalamus on FDG-PET.\(^56\)

**Amyloid Imaging in Progressive Supranuclear Palsy and Corticobasal Degeneration**
PSP and CBD are tauopathic neurodegenerative diseases that exhibit no amyloid deposition. If amyloid deposition is demonstrated with amyloid PET, it should be considered small amyloid deposits with age-related amyloid pathology or extended amyloid deposits similar to those in AD due to comorbidity of AD, which may be associated with \(APOE\) \(e4\).

**Idiopathic Normal Pressure Hydrocephalus**
Idiopathic normal pressure hydrocephalus is characterized by disproportionately enlarged cerebrospinal spaces, ventricle and Sylvian fissure dilation, and tight sulci at high convexity in the medial parietal sulci.\(^57\) To detect these features, morphologic images by using CT or MR imaging are necessary. On the other hand, functional images are not necessary because the glucose metabolic reduction pattern is heterogeneous in idiopathic normal pressure hydrocephalus.\(^58\) Glucose metabolism in idiopathic normal pressure hydrocephalus before and after a
shunt operation is promptly reversible after surgery, and there is a relationship between the early metabolic changes and clinical symptoms that is independent of the simultaneous changes in ventricular size.\(^5\) Because idiopathic normal pressure hydrocephalus occurs in elderly individuals, there is a possibility for concomitant AD. Amyloid imaging with PET may be useful to detect early concomitant AD and other diseases associated with amyloid deposits.\(^6\)

### Vascular Dementia

Vascular dementia is diagnosed with clinical symptoms and by detecting symptoms related to vascular lesions demonstrated by morphologic imaging. As such, pure vascular dementia is not a PET-applicable dementia. However, vascular dementia is sometimes associated with AD or other neurodegenerative pathology, and these patients should be examined with FDG-PET to determine the comorbidity of AD or other neurodegenerative pathology. Amyloid imaging can be used to remove the comorbidity of AD pathology when there is no amyloid deposit.

### Tau Imaging

After amyloid plaques, intracellular neurofibrillary tangles are an important hallmark of AD. Neurofibrillary tangles are preferentially located in the hippocampus and associative cortical regions. \(^14\)F-2-{1-[6-{2-[F]Fluoroethyl}(methyl)amino]-2-naphthyl}-ethylidene)malononitrile or FDDNP was initially developed for A\(\beta\) imaging, though this ligand binds to both A\(\beta\) plaques and neurofibrillary tangles in the brain. As such, FDDNP was expected to demonstrate both amyloid and neurofibrillary tangle deposits\(^6\) but has limited value for accurate measurement of \(\tau\)-related pathology in patients with AD. \(^18\)F-THK-523 was developed as a potential in vivo imaging probe for \(\tau\) pathology and was reported to accumulate in regions containing a high attenuation of \(\tau\) protein deposits.\(^6\) This tracer is now being used in patients with AD. Some forms of FTD, PSP, and CBD are also characterized by pathologic accumulation of \(\tau\) protein. Thus, \(\tau\) imaging will be useful in distinguishing these diseases from AD.

### Cost-Effectiveness of PET Imaging for Dementia

Silverman et al\(^6\) first evaluated the cost and benefit of the diagnosis of early AD by using FDG-PET and reported that appropriate use of FDG-PET can add valuable information to the clinical work-up, without adding to the overall costs of evaluation and management in the United States. In Europe, Moulin-Romsee et al\(^6\) reported that the introduction of FDG-PET into the clinical work-up of patients with suspected AD can result in substantial benefit in terms of health care cost savings and in benefit for the patient. For the present, there is still no radical treatment for AD because diagnosis of early or preclinical dementia remains controversial. Multicenter cohort studies should be performed to evaluate the cost-effectiveness of new biomarkers such as amyloid PET for early diagnosis of AD and other neurodegenerative dementias and to establish appropriate PET use criteria for the benefit of patients.

### CONCLUSIONS

The use of PET enables the early detection of pathophysiologic changes in patients with dementia and allows differential diagnosis among neurodegenerative dementias. A summary of FDG-PET and amyloid PET findings for each neurodegenerative dementia is shown in Table 2. Each disease has characteristic regional metabolic reduction patterns on FDG-PET. PET is now used as an in vivo imaging technique for examining neurodegenerative dementia including AD and for detecting the early symptomatic and preclinical stages of dementia.

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