NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

REVIEW

Arch Neuropsychiatry 2022; 59: (Supplement 1): S17–S23
https://doi.org/10.29399/npa.28155

What is New in Nuclear Medicine Imaging for Dementia

Esen SAKA TOPÇUOĞLU[1], Ümit Özgür AKDEMİR[2], Lütfiye Özlem ATAY[2]

[1]Hacettepe University Faculty of Medicine, Department of Neurology, Ankara, Turkey
[2]Gazi University Faculty of Medicine, Department of Nuclear Medicine, Ankara, Turkey

ABSTRACT

Advances in the molecular biology, pathology and genetics of Alzheimer's disease (AD) and other degenerative dementias have led to the development of biomarkers specific to these diseases and radiotracers that are used in nuclear medicine. Imaging and non-imaging markers have enabled very early recognition of these diseases and have caused significant changes in their definitions. Amyloid positron emission tomography (PET) and tau PET, which are molecular imaging methods, [F18]fluorodeoxyglucose (FDG) PET showing the glucose metabolism pattern in the brain, dopamine transporter single photon emission computerized tomography (SPECT) that marks dopaminergic terminals are valuable tools for early recognition and differentiation of AD and its atypical variants, frontotemporal dementias and dementia with Lewy bodies. These imaging methods, which have different advantages over each other, have different indications for use and sometimes provide complementary information. In addition, research on radiotracers targeting neuroinflammation, astrocytes, synaptic density, and cholinergic terminals is ongoing. In this review, routinely used and newly developed nuclear imaging methods in AD and other neurodegenerative dementias, the agents used and their diagnostic features will be presented together with case examples.

Keywords: Alzheimer's disease, amyloid, cognitive dysfunction, fluorodeoxyglucose F18, positron-emission tomography, tau proteins

Cite this article as: Saka Topçuoğlu E, Akdemir ÜÖ, Atay LÖ. What is New in Nuclear Medicine Imaging for Dementia. Arch Neuropsychiatry 2022; 59: (Supplement 1): S17–S23.

INTRODUCTION

Structural, functional and molecular imaging methods are being used increasingly in the diagnosis of dementing illnesses. Structural imaging information obtained by brain computed tomography (CT) and brain magnetic resonance imaging (MRI) primarily aims to distinguish secondary dementia causes such as subdural hematoma, brain tumor, normal pressure hydrocephalus, and also enables the recognition of atrophy patterns seen in different neurodegenerative diseases (1). In our clinical practice, evaluation of brain MRI images and brain CT images in cases where MRI cannot be performed is an indispensable approach in the diagnosis and differential diagnosis of dementia. On the other hand, nuclear imaging methods using single photon emission tomography (SPECT) and positron emission tomography (PET) provides increased specificity in diagnosis and differential diagnosis by enabling the detection of functional involvement patterns and molecular pathology in primary neurodegenerative dementias. In our clinical practice, these tests have been used more and more in cases where more clarity is needed in the differential diagnosis. In this review, nuclear medicine imaging methods used or developed in Alzheimer's disease (AD) and other neurodegenerative dementias, the agents used and their diagnostic features will be presented together with case examples.

Highlights

- **Alzheimer's disease specific changes can be detected at the earliest by amyloid PET.**
- **Tau PET is valuable in detecting severity of neurodegeneration in AD.**
- **Brain metabolic PET imaging with fluorodeoxyglucose predicts prognosis in mild cognitive impairment.**

Functional and Molecular Imaging in AD

The main feature in the pathology of AD is amyloid plaques formed as a result of pathological folding of amyloid beta peptide, and neurofibrillary tangles containing pathological folding and precipitation aggregation of tau protein (p-tau 217 and p-tau 181), which show increased phosphorylation in threonine 217 and threonine 181 regions. It is a widely accepted hypothesis with strong scientific evidence that amyloid accumulation starts first as a result of increased amyloid beta formation or decreased clearance in the pathogenesis of the disease, and then tau pathology accompanies amyloid accumulation which is triggered or increased by this pathology (2). Along with these protein pathologies, inflammation, synaptic dysfunction and ultimately synaptic and neuronal loss develop. It is known that the disease clinic, which is characterized by memory loss and other cognitive dysfunctions, appears at least 10-20 years after the onset of all these pathophysiological changes (3). This feature enables the diagnosis of AD by the determination of amyloid beta and tau protein accumulation even before the disease clinically becomes evident (in the preclinical stage). Molecular imaging methods have an increasing role in the early diagnosis and differential diagnosis of AD by using agents that label amyloid, tau, microglia and synaptic density (4). In addition, the anatomical location and temporal development of pathological involvement in AD are used by functional imaging methods that use glucose metabolism as a neuronal activity marker. In recent years, the identification and use of biomarkers in the diagnosis of AD has been increasing. The aim is to provide early and accurate diagnosis of typical

Correspondence Address: Esen Saka Topçuoğlu, Maidan İş Merkezi, B-blok, 146 no'lu ofis, Mustafa Kemal Mah. Ankara, Turkey • **E-mail:** esensaka@gmail.com
Received: 13.03.2022, **Accepted:** 02.04.2022, **Available Online Date:** 16.12.2022

or atypical forms of the disease. For this purpose, A/T/N classification scheme has been developed and in this scheme, amyloid PET, tau PET and [F18] fluorodeoxyglucose (FDG) PET, which are among the AD imaging methods, are included as amyloid biomarker, tau biomarker and neurodegeneration biomarker, respectively (5). Similarly, the AD international working group and NIA-AA criteria defined amyloid PET as a pathophysiological biomarker and amyloid beta biomarker, and FDG PET as a topographic marker and neuronal damage marker, respectively (6,7). Thus, preclinical AD, prodromal AD and AD dementia (ADD), which constitute different stages of the same disease and are also defined as the AD continuum can be confirmed and each stage can be effectively recognized by biomarkers. Early diagnosis is key for early treatment, which then may prevent the transformation into dementia and may also determine the prognosis.

Amyloid PET imaging

With the development of agents that bind to amyloid beta much earlier, the first molecular imaging method used in the early diagnosis and differential diagnosis of AD was amyloid PET. This method allows visualization of amyloid plaques and fibrils in the brain (8). [18F] FDDNP and [11C] PiB were the first radiomarkers to be developed. [18F] FDDNP could not be carried into clinical trials because it does not bind specifically to amyloid beta. [11C] PiB has been extensively studied. However, it is not suitable for widespread clinical use due to the short half-life of radioactive carbon-11 (approximately 20 minutes) (9). The second generation agents used for amyloid PET imaging are [18F] florbetaben, [18F] flutemetamol, [18F] BF-227, [18F] florbetapir, [11C] BF22752, and [11C] SB-13 (10). Three of these agents, [18F] florbetaben, [18F] flutemetamol and [18F] florbetapir, have been approved for use in the diagnosis of AD by the US Food and Drug Administration (FDA) in the United States, and the European Medicines Agency (EMA) in Europe. More specific amyloid binding is aimed with third generation agents, including [18F] NAV4694 (AZD4694), [18F] FPYBF-2, [18F] FIBT, [18F] FC119S, [18F] FACT, and [11C] AZD2184 (10).

Studies, mostly with second-generation agents and [11C] PiB, have shown that amyloid PET imaging does not show significant cortical involvement other than white matter tracer retention in normal individuals (Figure 1a, 1e), whereas in AD, the posterior cingulate cortex, prefrontal cortex, and striatum are typically associated with increased retention of amyloid-binding agents (11). Centiloid scale was developed for the comparative evaluation of amyloid PET imaging performed with all these agents and for the establishment of standardization between centers (12). Amyloid binding features are similar in the preclinical stage of AD, in the prodromal stage (mild cognitive impairment (MCI) in AD continuum) and ADD, but the intensity of amyloid tracer uptake may differ (Figure 1b–1d, 1f–1h). Although the intensity of amyloid tracer retention increases gradually from the preclinical stage to the ADD stage, it is known that this increase does not continue and reaches a plateau in ADD.

Similar to the findings obtained in pathology studies, the presence of cortical amyloid deposition has been demonstrated by amyloid PET imaging in elderly individuals who were evaluated as cognitively normal, and this rate has been reported as 10–44% in different studies (13). According to the A/T/N classification system, these individuals are defined as preclinical AD. On the other hand, amyloid PET imaging showed no amyloid accumulation in 20–30% of patients diagnosed and treated as ADD, and in 30-50% of patients diagnosed as MCI in dementia clinics (14). All these findings reveal that if amyloid PET is put into routine clinical use, it can cause a 60% change in patient treatment and follow-up (15,16).

Although the clinical indications for amyloid PET imaging have not been fully determined, the indications recommended by the Amyloid Imaging Working Group are differential diagnosis in atypical cases (such as early age of disease onset, atypical clinical features), situations where early diagnosis is required (amyloid-based treatment plan), and investigational use (17). The amyloid involvement imaging features mentioned above are seen in both the typical presentation and atypical presentations of the disease (posterior cortical atrophy, logopenic variant AD or frontal-executive variant AD). It is important to differentiate whether these specific phenotypes, each of which can be associated with more than one pathology and disease, are due to AD, to decide on the treatment method and to determine the prognosis. For example, posterior cortical atrophy may be associated with AD, corticobasal degeneration, dementia with Lewy bodies, or prion disease. Although structural brain imaging or FDG PET imaging may show similar findings regardless of the underlying pathology, the detection of the underlying disease can only be achieved by recognizing amyloid beta, tau or alpha-synuclein deposition by molecular imaging. Figure 1 (1d, 1h) shows the FDG PET examination imaging findings of a case of atypical AD with clinical features of posterior cortical atrophy, and amyloid deposition with the [18F] flutemetamol radiotracer.

In the diagnosis of AD, cerebrospinal fluid (CSF) markers (Abeta42, Abeta42/Abeta40 ratio, total tau and phosphorylated tau) have been developed and in clinical use even earlier than amyloid iamging (18,19). Although measurement of CSF markers has a lower cost compared to PET imaging, the disadvantages of these markers include the need for lumbar puncture (LP), which is a relatively invasive procedure, presence of contraindication of LP such as in patients receiving anticoagulant therapy, lower sensitivity (80–86% vs 91–98%) and specificity (77–82% vs 87–100%) and not providing information about the density and regional distribution of amyloid deposition (4). This latter feature also makes amyloid PET imaging more valuable in monitoring response to therapy.

Tau PET imaging

Different agents that bind to tau protein are being developed to monitor tau accumulation in AD and other degenerative diseases with tau accumulation such as frontotemporal dementias (eg. Pick's disease), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD), which are also defined as taupathies. The presence of different isoforms of the tau protein, the accumulation of tau within the cell, and the low amount of accumulation in general make tau imaging more difficult than amyloid imaging (20). Among the tau-binding agents, [18F] THK5351, [18F] THK5317, [18F] AV1451 (Flortaucipir), [11C] PBB3 are first generation agents, and their specific and non-specific binding properties to pathological tau accumulation in AD have been investigated in detail. In clinical studies in which antemortem tau PET imaging and postmortem tau immunohistochemistry in AD are performed in short time period, in addition to their binding to pathological tau accumulation, the first generation agents have been shown to bind to choroid plexus, dural venous sinuses, myelin protein and white matter, neuromelanin, and even other pathologically folded proteins alpha-synuclein and TDP-43, monoamine-oxidase (MAO) A and B, and glial fibrillary acidic protein (GFAP) (21). Their binding to the MAO enzyme causes nonspecific involvement of brain regions (eg basal ganglia) that highly express this enzyme (20). In addition, targeting GFAP, a marker of astrocytosis, indicates that these agents may also be a marker of inflammation.

[18F] Flortaucipir has been approved by the FDA for the imaging of AD (22). In addition to the non-specific binding properties mentioned above, it can recognize tau accumulation in AD in accordance with the Braak staging system, and shows sufficient reliability in the early diagnosis of AD, in its differentiation from MCI and normal controls, and in staging dementia (23–26). Consistent with the Braak staging of tau pathology (26), the imaging study performed in 173 MCI and AD patients revealed

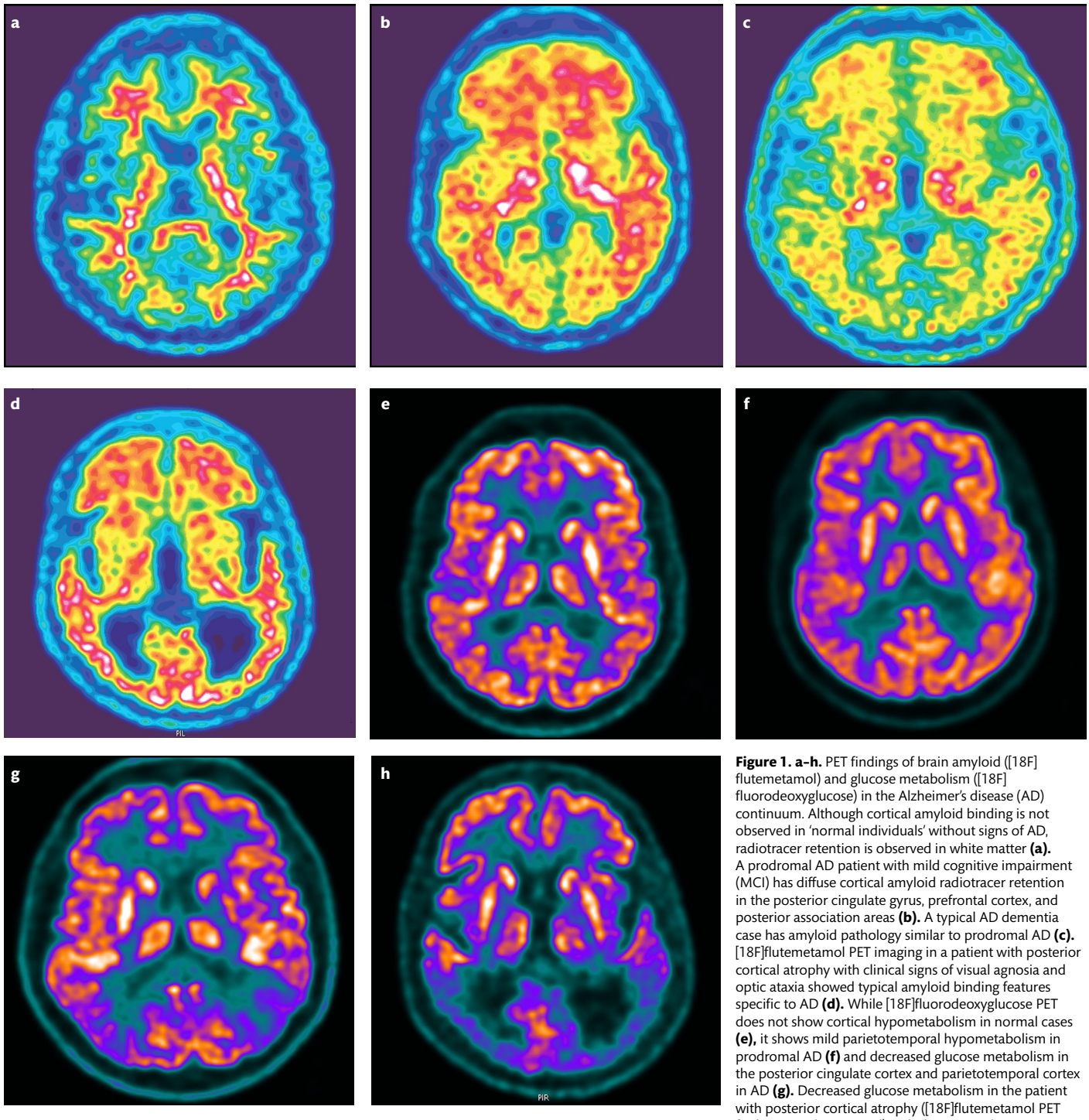

Figure 1. a–h. PET findings of brain amyloid ([18F] flutemetamol) and glucose metabolism ([18F] fluorodeoxyglucose) in the Alzheimer's disease (AD) continuum. Although cortical amyloid binding is not observed in 'normal individuals' without signs of AD, radiotracer retention is observed in white matter **(a).** A prodromal AD patient with mild cognitive impairment (MCI) has diffuse cortical amyloid radiotracer retention in the posterior cingulate gyrus, prefrontal cortex, and posterior association areas **(b).** A typical AD dementia case has amyloid pathology similar to prodromal AD **(c).** [18F]flutemetamol PET imaging in a patient with posterior cortical atrophy with clinical signs of visual agnosia and optic ataxia showed typical amyloid binding features specific to AD **(d).** While [18F]fluorodeoxyglucose PET does not show cortical hypometabolism in normal cases **(e),** it shows mild parietotemporal hypometabolism in prodromal AD **(f)** and decreased glucose metabolism in the posterior cingulate cortex and parietotemporal cortex in AD **(g).** Decreased glucose metabolism in the patient with posterior cortical atrophy ([18F]flutemetamol PET findings are shown in 1d) includes occipital association areas in addition to the temporoparietal cortex **(h).**

that tau pathology was first seen in the entorhinal cortex in the medial temporal lobe in asymptomatic cases, then consistent with clinical progression it progressed towards the hippocampus and fusiform cortex, middle temporal gyrus, precuneus, superior temporal cortex, and other cortical areas (23). This feature of extension also supports the hypothesis that tau pathology spreads prion-like propagation (27). It has been shown that tau pathology increases as the disease progresses, unlike amyloid beta accumulation dynamics, and does not plateau like amyloid beta (28).

With the new generation tau agents under development, non-tau protein binding ("off-target binding") can be significantly reduced. The most studied of these agents are [18F] PM-PBB3, [18F] MK-6240, [18F] PI-2620, [18F] RO-948, and [18F] GTP-1 (21). It has been shown that second generation tau radiomarkers bind specifically in regions where tau pathology is seen in AD, such as the medial temporal lobe, precuneus/posterior cingulate cortex, lateral parietal and prefrontal cortex (21).

Studies with different agents have shown that tau PET imaging findings overlap with areas of brain hypometabolism; predicts clinical severity and cognitive impairment more than other imaging studies such as structural imaging or amyloid imaging (29). In addition, tau accumulation and tau radiolabeling are seen in different phenotypes of AD in clinically compatible anatomical structures (30).

FDG PET imaging

FDG PET imaging reveals glucose metabolism changes in the brain due to decreased glutamatergic synaptic activity. Differences in brain structures affected in neurodegenerative dementias cause different regional glucose hypometabolism patterns. In the typical form of AD, a decrease in glucose metabolism of the posterior cingulate cortex/precuneus and temporoparietal cortices is observed (Figure 1g). Although the sensitivity and specificity of this typical pattern in distinguishing AD from other dementias vary in different studies, it was determined as 90% and 89%, respectively, in a meta-analysis study that included large number of studies (31). In atypical presentations of AD, the typical involvement pattern is often accompanied by frontal cortical hypometabolism (frontal-executive variant AD), perisylvian hypometabolism in the dominant hemisphere (logopenic variant AD), or occipital cortical hypometabolism (posterior cortical atrophy) (Figure 1h). These changes occur in the AD continuum, in the MCI stage, and can be detected before the development of atrophy that can be detected by structural imaging (32). Therefore, the use of FDG PET imaging is recommended for the early diagnosis of AD (MCI in the AD continuum), for distinguishing AD from other dementias, and even for staging clinical severity (3).

Many recent studies have shown that FDG PET imaging is also very valuable in determining the short- and long-term prognosis of MCI patients. The conversion of MCI patients to ADD was predicted incorrectly at a rate of 32% when only CSF markers or brain MRI evaluations were used, and the rate of incorrect prediction was 27% when these examinations were used together; however, it was observed that this rate decreased to 9% if FDG PET was also included in the evaluation (33). It is known that amyloid PET can predict the conversion of MCI to ADD with a high probability. If amyloid PET and FDG PET are compared in this regard, FDG PET predicts cognitive decline and conversion to ADD in the short term with higher specificity than amyloid PET (34,35). In Figure 2, we present two cases of prodromal AD (MCI) with [18F] flutemetamol and FDG PET imaging findings. Their imaging findings constitute a typical example showing the prognostic value of FDG PET. Although the duration of education, age and cognitive findings of both cases were quite similar, it was observed that in case 1, a rapid deterioration and conversion to ADD was observed after 2 years of follow-up, and in case 2, clinical deterioration did not occur within a similar time period. Although [18F] flutemetamol PET imaging features of case 1 and case 2 (Figure 2a and 2c, respectively) were quite similar and showed typical AD retention pattern, FDG PET findings (significant bilateral temporo-parietal and posterior cingulate cortex hypometabolism in case 1; normal glucose metabolism in case 2) differed (Figure 2b and 2d, respectively).

Other molecular imaging modalities under development

Imaging modalities targeting other changes in AD pathogenesis include synaptic vesicle glycoprotein 2A (SV2A) imaging (36), which shows the change in synaptic density; agents that mark translocator protein 18kDA (TPSO), a marker of neuroinflammation or microglia activation, such as [11C] PK11195, [11C] PBR28, [18F] DPA-714, [18F] EPPA, [11C] DAA1106; [11C] deuterium-L-deprenyl PET (14), which binds to MAO B expressed by active astrocytes, and others that we could not include in this review. These imaging agents are not yet in clinical use.

Molecular and Functional Imaging in Other Degenerative Dementias

Molecular imaging

The most common degenerative dementia after AD is dementia with Lewy bodies (LBD) (37). Lewy body is a common pathology in LBD, Parkinson's disease and Parkinson's disease dementia, and the main constituent of Lewy body is alpha-synuclein. Although the development of alpha-synuclein-binding agents in the molecular imaging of these diseases is ongoing, these agents have not yet been brought into clinical use. Because AD pathology frequently accompanies LBD and Parkinson's disease dementia, amyloid PET imaging can be positive or negative depending on co-occurance of AD pathology (1). However, visualization of the loss of dopamine transporter (DAT) in dopaminergic terminals, which is the common biochemical feature of these diseases, is an imaging marker that supports the diagnosis of LBD or Parkinson's disease dementia and can distinguish it from AD (38). [123I] Ioflupane (DaTScan™) SPECT is the most widely used molecular imaging modality that enables imaging of active dopaminergic synapses in the striatum. It provides visualization of dopaminergic deficiency in the straitum in diseases such as Parkinson's disease and LBD, which are associated with loss of dopaminergic neurons. However, it is recommended that drugs that may affect the dopaminergic system such as bupropion, fentanyl and anesthetics be discontinued for certain periods before taking images, as they may change the imaging findings (39). [18F] DOPA PET shows dopa decarboxylase activity, which will lead to the uptake of dopa and its conversion to dopamine in dopaminergic nerve terminals. Although less used than DAT imaging, [18F] DOPA PET is a helpful method in the diagnosis of LBD, Parkinson's disease and Parkinson's disease dementia (14).

Frontotemporal dementias (FTD) have different phenotypic, genetic and molecular subtypes. Clinically, the most common forms of FTD are behavioral variant FTD, semantic variant FTD with impaired single-word comprehension and semantic information, progressive nonfluent aphasia variant FTD, CBD, and PSP. Molecularly, tau pathology (may show 3R or 4R tau pathology), TDP-43 pathology or FUS pathology can be seen in different phenotypic forms. TDP-43 or FUS PET imaging has not yet been developed.

Tau pathology is seen in FTD with tau accumulation (tau pathology is a dominant pathology in patients with behavioral variant FTD and progressive nonfluent aphasia variant FTD), CBD, PSP, Down syndrome, chronic traumatic encephalopathy, and many other diseases, and the diagnostic value of tau PET imaging in these diseases is being investigated. [18F] flortaucipir, which has been shown to be of diagnostic importance in AD, a 3R/4R taupathy, failed to show reliable diagnostic utility in other taupathies with pure 3R or 4R tau deposition (40). On the other hand, the anatomical location and distribution characteristics of tau pathology in different diseases have been demonstrated by studies with different tau-binding agents. One of the second-generation tau radiomarkers [18F] PI-2620 shows highly specific tau binding in the basal ganglia and other subcortical areas affected by the disease in PSP (41). [18F] PI-2620 was able to show cortical involvement in CBD, which is also a 4R taupathy. Although studies on many different radiotracers are still in progress, no agent has yet been able to demonstrate diagnostic efficiency and approval for use in taupathies other than AD.

In addition, dopaminergic deficiency can be visualized by DAT imaging in CBD and PSP diseases, which are atypical parkinsonian syndromes (14).

FDG PET imaging

The typical pattern seen on LBD but with relatively limited sensitivity is glucose hypometabolism in the bilateral parietooccipital cortex that excludes the posterior cingulate gyrus (cingulate island sign) (38,42).

The pattern of hypometabolic activity in FTD reflects the pattern of atrophy seen in different subtypes: the frontal lobes, anterior temporal lobes, insula, anterior cingulate gyrus, and thalamus are the areas affected. In behavioral variant FTD, the prefrontal cortex and anterior cingulate cortex; in the semantic variant FTD, the anterior temporal cortices (Figures 3a and 3b) which is more prominent on the left; in the progressive nonfluent aphasia variant, the frontal (lateral-posterior,

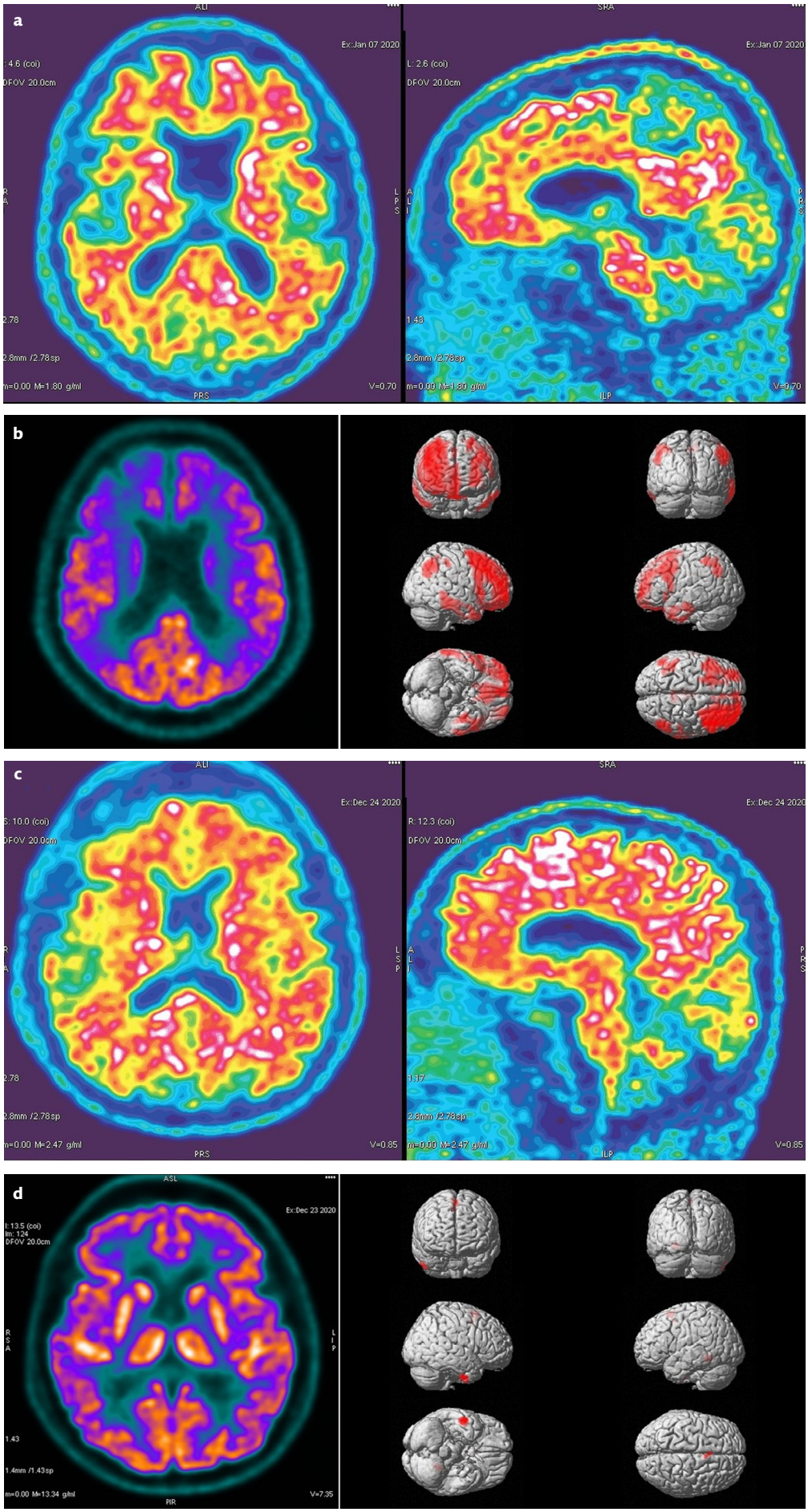

Figure 2. a–d Comparative [18F]flutemetamol and [18F] fluorodeoxyglucose PET images of two mild cognitive impairment (MCI) patients with different clinical courses. In case 1, a 68-year-old male university graduate, standardized mini mental test score (MMSE): 29, enhanced cued recall (ECR) test score: 46 (memory test, N>42) at the time of PET/MR imaging (a and b) were obtained. [18F] flutemetamol PET imaging of this patient showed intense amyloid beta tracer retention in the brain **(a).** [18F] fluorodeoxyglucose PET imaging revealed significant glucose hypometabolism in the posterior cingulate cortex and bilateral parietotemporal cortices **(b).** These findings are seen both in the visual evaluation of PET and in the quantitative analysis performed with the statistical parametric mapping (SPM) method. In the SPM analysis, the brain PET image normalized to the patient's MNI atlas is compared with the normal [18F] fluorodeoxyglucose PET database, and areas with statistically significant hypometabolism are topographically shown on the brain MR image. In the clinical evaluation of this patient 2 years later, significant cognitive decline occurred, and the MMSE score was evaluated as 15. In case 2, a 64-year-old, university graduate male patient, when PET/MR images were obtained **(c and d),** his cognitive status was very similar to case 1 (MMSE score: 29, ECR score: 47). [18F]flutemetamol PET imaging of this patient showed overt amyloid beta tracer retention **(c),** and [18F]fluorodeoxyglucose PET imaging revealed normal glucose metabolism **(d).** No clinical regression (disease progression) was observed in the 2-year follow-up of case 2.

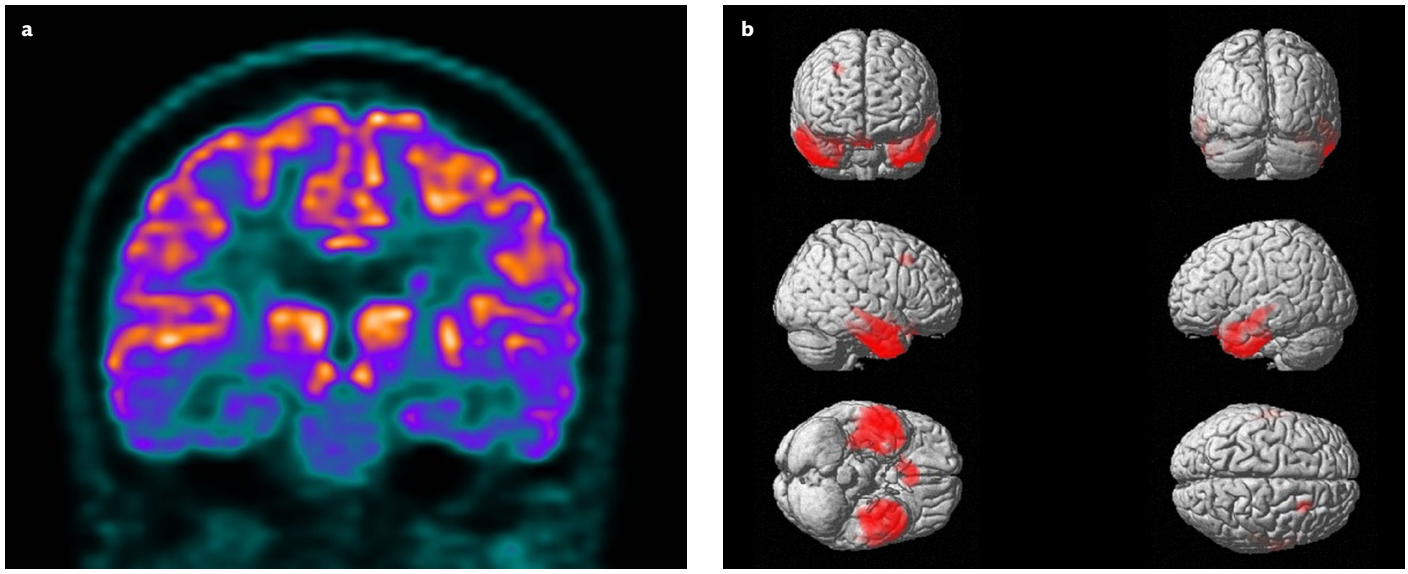

Figure 3. a, b. [18F] fluorodeoxyglucose PET/MR imaging findings in semantic variant frontotemporal dementia. A 58-year-old female patient was seen due to 7 years of progressive tactlessness, lack of empathy, and naming problems for rarely used objects. In the coronal cross-section image of PET, glucose hypometabolism in the temporal cortices (left>right) and frontal cortex of the patient is evident, patient's brain MRI showed frontotemporal (especially in the left anterior temporal cortex) cortical atrophy, **(a)** these findings are also evident in the quantitative analysis performed by SPM method **(b).**

superior-medial) and anterior temporal lobes, the insula and the angular gyrus which are more prominent on the left are known to be particularly affected by glucose hypometabolism (43,44).

As a conclusion, molecular and functional imaging methods in AD and other degenerative dementias are being developed at an increasing rate for research and clinical use. These imaging methods, which show the pathophysiological molecules of the diseases, the detection of neurochemical changes and the anatomical selectivity of the disease-specific neurodegeneration, can contribute to early diagnosis, determination of the prognosis and clarification of the diagnosis. Today, when treatments aiming for halting the pathogenesis of the disease are being developed rapidly, these imaging studies are essential for early and accurate diagnosis and access to effective treatment.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – EST, LÖA; Design – EST, ÜÖA, LÖA; Supervision – EST, LÖA; Resource – LÖA; Material - EST, LÖA; Data Collection and/or Processing - EST, ÜÖA,LÖA; Analysis and/or Interpretation - EST, ÜÖA, LÖA; Literature Search – EST, ÜÖA; Writing – EST; Critical Appraisal – ÜÖA, LÖA.

Conflict of Interests: The authors declared that there is no conflict of interest.

Financial Disclosure: The authors of this article do not have any financial support.

REFERENCES

1. Patel KP, Wymer DT, Bhatia VK, Duara R, Rajadhyaksha CD. Multimodality imaging of dementia: clinical importance and role of integrated anatomic and molecular imaging. Radiographics. 2020;40(1):200–222. [Crossref]
2. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. Embo Mol Med. 2016;8(6):595–608. [Crossref]
3. Knopman DS, Amieva H, Petersen RC, Chetelat G, Holtzman DM, Hyman BT, et al. Alzheimer disease. Nat Rev Dis Primers. 2021;7(1):33. [Crossref]
4. Chetelat G, Arbizu J, Barthel H, Garibotto V, Law I, Morbelli S, et al. Amyloid-PET and 18F-FDG-PET in the diagnostic investigation of Alzheimer's disease and other dementias. Lancet Neurol. 2020;19(11):951–962. [Crossref]
5. Jack Jr CR, Bennett DA, Blennow K, Carrillo MC, Feldman HH, Frisoni GB, et al. A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology. 2016;87(5):539–547. [Crossref]
6. Dubois B, Feldman HH, Jacova C, Harald Hampel, José Luis Molinuevo, Kaj Blennow, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 2014;13(6):614–629. [Crossref]
7. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack Jr CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):263–269. [Crossref]
8. Villemagne VL, Dore V, Burnham SC, Masters CL, Rowe CC. Imaging tau and amyloid-beta proteinopathies in Alzheimer disease and other conditions. Nat Rev Neurol. 2018;14(4):225–236. [Crossref]
9. Klunk WE, Engler H, Nordberg A, Wang YM, Blomqvist G, Holt DP, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol. 2004;55(3):306–319. [Crossref]
10. van Waarde A, Marcolini S, de Deyn PP, Dierckx RA. PET agents in dementia: an overview. Semin Nucl Med. 2021;51(3):196–229. [Crossref]
11. Catafau AM, Bullich S. Amyloid PET imaging: applications beyond Alzheimer's disease. Clin Transl Imaging. 2015;3(1):39–55. [Crossref]
12. Klunk WE, Koeppe RA, Price JC, Benzinger TL, Devous Jr MD, Jagust WJ, et al. The Centiloid Project: Standardizing quantitative amyloid plaque estimation by PET. Alzheimers Dement. 2015;11(1):1–15. [Crossref]
13. Jansen WJ, Ossenkoppele R, Knol DL, Tijms BM, Scheltens P, Verhey FR, et al. Prevalence of Cerebral Amyloid Pathology in Persons Without Dementia A Meta-analysis. Jama-J Am Med Assoc. 2015;313(19):1924–1938. [Crossref]
14. Villemagne VL, Barkhof F, Garibotto V, Landau SM, Nordberg A, van Berckel BN. Molecular imaging approaches in dementia. Radiology. 2021;298(3):517–530. [Crossref]
15. Fantoni ER, Chalkidou A, O'Brien JT, Farrar G, Hammers A. A systematic review and aggregated analysis on the impact of amyloid PET brain imaging on the diagnosis, diagnostic confidence, and management of patients being evaluated for Alzheimer's disease. J Alzheimers Dis. 2018;63(2):783–796. [Crossref]
16. Rabinovici GD, Gatsonis C, Apgar C, Chaudhary K, Gareen I, Hanna L, et al. Association of Amyloid Positron Emission Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia. JAMA. 2019;321(13):1286–1294. [Crossref]
17. Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, et al. Appropriate use criteria for amyloid PET. A report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. Alzheimers Dement. 2013;9(1): E1–E16. [Crossref]
18. Molinuevo JL, Ayton S, Batrla R, Bednar MM, Bittner T, Cummings J, et al. Current state of Alzheimer's fluid biomarkers. Acta Neuropathol. 2018;136(6):821–853. [Crossref]
19. Blennow K, Zetterberg H. Biomarkers for Alzheimer's disease: current status and prospects for the future. J Intern Med. 2018;284(6):643–663. [Crossref]

20. Leuzy A, Chiotis K, Lemoine L, Gillberg P-G, Almkvist O, Rodriguez-Vieitez E, et al. Tau PET imaging in neurodegenerative tauopathies-still a challenge. Mol Psychiatry. 2019;24(8):1112–1134. [Crossref]
21. Beyer L, Brendel M. Imaging of tau pathology in neurodegenerative diseases: an update. Semin Nucl Med. 2021;51(3):253–263. [Crossref]
22. Fleisher AS, Pontecorvo MJ, Devous Sr MD, Lu M, Arora AK, Truocchio SP, et al. Positron emission tomography imaging with [F-18]flortaucipir and postmortem assessment of Alzheimer disease neuropathologic changes. JAMA Neurol. 2020;77(7):829–839. [Crossref]
23. Schwarz AJ, Yu P, Miller BB, Shcherbinin S, Dickson J, Navitsky M, et al. Regional profiles of the candidate tau PET ligand 18F-AV-1451 recapitulate key features of Braak histopathological stages. Brain. 2016;139:1539–1550. [Crossref]
24. Johnson KA, Schultz A, Betensky RA, Becker JA, Sepulcre J, Rentz D, et al. Tau Positron Emission Tomographic Imaging in Aging and Early Alzheimer Disease. Ann Neurol. 2016;79(1):110–119. [Crossref]
25. Wang L, Benzinger TL, Su Y, Christensen J, Friedrichsen K, Aldea P, et al. Evaluation of tau imaging in staging Alzheimer disease and revealing interactions between beta-amyloid and tauopathy. JAMA Neurol. 2016;73(9):1070–1077. [Crossref]
26. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. Acta Neuropathol. 1991;82(4):239–259. [Crossref]
27. Goedert M, Clavaguera F, Tolnay M. The propagation of prion-like protein inclusions in neurodegenerative diseases. Trends Neurosci. 2010;33(7):317–325. [Crossref]
28. Pontecorvo MJ, Devous Sr MD, Navitsky M, Lu M, Salloway S, Schaerf FW, et al. Relationships between flortaucipir PET tau binding and amyloid burden, clinical diagnosis, age and cognition. Brain. 2017;140(3):748–763. [Crossref]
29. Ossenkoppele R, Smith R, Mattsson-Carlgren N, Groot C, Leuzy A, Strandberg O, et al. Accuracy of tau positron emission tomography as a prognostic marker in preclinical and prodromal Alzheimer disease: a head-to-head comparison against amyloid positron emission tomography and magnetic resonance imaging. JAMA Neurol. 2021;78(8):961–971. [Crossref]
30. Graff-Radford J, Yong KX, Apostolova LG, Bouwman FH, Carrillo M, Dickerson BC, et al. New insights into atypical Alzheimer's disease in the era of biomarkers. Lancet Neurol. 2021;20(3):222–234. [Crossref]
31. Bloudek LM, Spackman DE, Blankenburg M, Sullivan SD. Review and meta-analysis of biomarkers and diagnostic imaging in Alzheimer's disease. J Alzheimers Dis. 2011;26(4):627–645. [Crossref]
32. Laforce Jr R, Tosun D, Ghosh P, Lehmann M, Madison CM, Weiner MW, et al. Parallel ICA of FDG-PET and PiB-PET in three conditions with underlying Alzheimer's pathology. Neuroimage Clin. 2014;4:508–516. [Crossref]
33. Shaffer JL, Petrella JR, Sheldon FC, Choudhury KR, Calhoun VD, Coleman RE, et al. Predicting cognitive decline in subjects at risk for Alzheimer disease by using combined cerebrospinal fluid, MR imaging, and PET biomarkers. Radiology. 2013;266(2):583–591. [Crossref]
34. Caroli A, Prestia A, Galluzzi S, Ferrari C, van der Flier WM, Ossenkoppele R, et al. Mild cognitive impairment with suspected nonamyloid pathology (SNAP) Prediction of progression. Neurology. 2015;84(5):508–515. [Crossref]
35. Blazhenets G, Ma YL, Sörensen A, Schiller F, Rücker G, Eidelberg D, et al. Predictive value of 18F-florbetapir and 18F-FDG PET for conversion from mild cognitive impairment to Alzheimer dementia. J Nucl Med. 2020;61(4):597–603. [Crossref]
36. Cai Z, Li S, Matuskey D, Nabulsi N, Huang Y. PET imaging of synaptic density: a new tool for investigation of neuropsychiatric diseases. Neurosci Lett. 2019;691:44–50. [Crossref]
37. Yang S-K, Chen W, Su C-H, Liu C-H. Incidence and comorbidity of dementia with Lewy bodies: a population-based cohort study. Behav Neurol. 2018;2018:7631951. [Crossref]
38. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor J-P, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology. 2017;89(1):88–100. [Crossref]
39. Akdemir ÜÖ, Bora Tokçaer A, Atay LÖ. Dopamine transporter SPECT imaging in Parkinson's disease and parkinsonian disorders. Turk J Med Sci. 2021;51(2):400–410. [Crossref]
40. Soleimani-Meigooni DN, Iaccarino L, La Joie R, Baker S, Bourakova V, Boxer AL, et al. 18F-flortaucipir PET to autopsy comparisons in Alzheimer's disease and other neurodegenerative diseases. Brain. 2020;143(11):3477–3494. [Crossref]
41. Lyoo CH, Cho H, Choi JY, Ryu YH, Lee MS. Tau positron emission tomography imaging in degenerative Parkinsonisms. J Mov Disord. 2018;11(1):1–12. [Crossref]
42. Caminiti SP, Sala A, Iaccarino L, Beretta L, Pilotto A, Gianolli L, et al. Brain glucose metabolism in Lewy body dementia: implications for diagnostic criteria. Alzheimers Res Ther. 2019;11. [Crossref]
43. Minoshima S, Mosci K, Cross D, Thientunyakit T. Brain [F-18]FDG PET for clinical dementia workup: differential diagnosis of Alzheimer's disease and other types of dementing disorders. Semin Nucl Med. 2021;51(3):230–240. [Crossref]
44. Guedj E, Varrone A, Boellaard R, Albert NL, Barthel H, van Berckel B, et al. EANM procedure guidelines for brain PET imaging using [18F]FDG, version 3. Eur J Nucl Med Mol Imaging. 2022;49(2):632–651. [Crossref]