Clinical and Translational Imaging (2020) 8:127–140
https://doi.org/10.1007/s40336-020-00366-0

EXPERT REVIEW

Current role of 18F-FDG-PET in the differential diagnosis of the main forms of dementia

Edgar F. Guillén[1] · Juan J. Rosales[2] · Darío Lisei[3] · Fabiana Grisanti[2] · Mario Riverol[4] · Javier Arbizu[2]

Received: 26 February 2020 / Accepted: 20 April 2020 / Published online: 7 May 2020

Abstract

Purpose We aim to present and critically evaluate the use of FDG-PET in the differential diagnosis between dementing conditions including Alzheimer disease (AD), frontotemporal dementia (FTD) and its variants, vascular dementia (VaD) and pseudodepressive dementia.

Methods This review is based on the available consensus recommendations for the use of FDG-PET and current clinical diagnostic criteria. In addition, we updated these reviews with relevant publications in the field after conducting a literature search during the last 5 years through predefined keyword strings relating to the specific terms related to the diseases covered in this review and a common part ('FDG-PET').

Results Neurodegenerative disease are complex groups of several forms of dementia and their clinical diagnostic criteria are progressively incorporating imaging biomarkers as a supporting tool. The role of FDG-PET is currently increasing as part of the clinical practice supporting the clinical diagnosis of AD (at both mild cognitive impairment—MCI—and early dementia stages), FTD and its variants, as well as VaD and pseudodepressive dementia. The pattern of AD is well defined and its negative predicted value may help the differential diagnosis when comorbidities like vascular disease or depression are present. However, the formal evidence supporting the use of FDG-PET is reasonable for MCI due to AD, and the differential diagnosis between FTD and AD, but lacking for the remaining clinical uses. Interestingly, the evidence provided during the last years reinforces these recommendations and gives additional clues about the usefulness of semiquantitative methods in addition to visual reading.

Conclusion The large experience accumulated using FDG-PET for the differential diagnosis of the main conditions with dementia has been translated into more formal evidence to support its clinical use. Although FDG-PET form currently part of the clinical practice in many countries, there is still a lack of studies using standardized analysis that confirm specific patterns at individual level.

Keywords 18F-FDG · PET · Differential diagnosis · Mild cognitive impairment · Alzheimer's disease · Frontotemporal lobar degeneration · Primary progressive aphasia · Vascular dementia · Pseudodementia

Introduction

18F-Fluorodeoxiglucose (FDG) enables the evaluation of changes in synaptic glucose consumption that occur in response to neuronal dysfunction secondary to pathological phenomena, even before cell death and atrophy take place [1, 2]. FDG was one of the first radiotracers used for brain PET scans and currently is the most available PET radiotracer worldwide.

The large experience accumulated using FDG-PET led the scientific societies and working groups to include this topographical biomarker of neuronal injury as a main or supportive feature in the clinical diagnostic criteria of many

✉ Javier Arbizu
jarbizu@unav.es

[1] Department of Nuclear Medicine, Clínica Universidad de Navarra, Madrid, Spain

[2] Department of Nuclear Medicine, Clínica Universidad de Navarra, Pamplona, Spain

[3] Department of Nuclear Medicine, Hospital Universitario Central de Asturias, Oviedo, Spain

[4] Department of Neurology, Clínica Universidad de Navarra, Pamplona, Spain

neurodegenerative conditions associated with dementia. Therefore, FDG-PET is integrated in the diagnostic workup of dementing disorders in different countries [3]. However, until recently, comprehensive clinical guidelines or recommendations on when and why to use FDG-PET in neurodegenerative diseases were not available. The European Association of Nuclear Medicine (EANM) and the European Academy of Neurology (EAN) agreed to launch a joint initiative providing guidance to clinicians on the indications for the brain FDG-PET. The initiative included a set of clinical questions to be addressed based on literature evidence (last update November 2015) and expert consensus [4].

Current proposed diagnostic criteria for Alzheimer's Disease (AD) [5, 6], considered the disease as a "continuum". It starts with a preclinical phase during which the physiopathological processes inherent to AD are already present, followed by an early symptomatic phase named prodromal or mild cognitive impairment (MCI) stage [7], and ultimately, the phase of dementia that represents a late stage of the disease. Clinical diagnosis of AD can raise doubts in specialists and patients' minds, mostly at the MCI or prodromal stages, but also in the dementia stage. These are essentially cases that conform to a diagnosis of possible AD (NIA-AA criteria) [5] or atypical (IWG-2 criteria) [6] or mixed AD (IWG-2 criteria). Such cases include patients in whom AD is clinically suspected but whose onset pattern is not typical (acute start, prolonged stable course), or there is suspected co-pathology like vascular or Lewy Body Dementia (LBD). Atypical AD criteria from the IWG-2 refer to atypical AD clinical presentations (frontal, logopenic aphasia or posterior cortical presentations), whereas in IWG-2 mixed AD, the patient fulfils both AD criteria and the criteria for the coexisting disease that is contributing to the cognitive condition (vascular pathology, LBD). In this context, it is worth noting that the clinical diagnostic criteria recognize the importance of biomarkers in the diagnosis of AD. Moreover, the present consensus criteria for the clinical diagnosis of the behavioural and language variants (non-fluent aphasia, semantic dementia and logopenic aphasia) of frontotemporal dementia (FTD) include neuroimaging biomarkers as supplementary criteria [8, 9].

The use of structural imaging, computed tomography (CT) or magnetic resonance imaging (MRI), form part of the initial approach for the assessment of patients with cognitive impairment. They can rule out secondary causes (vascular, tumour, etc.), and enable the evaluation of the neuronal lesion based on the degree of atrophy (particularly of medial temporal atrophy), which correlates with the neuropathological findings, and with the severity and progression of the disease. However, their sensitivity for the diagnosis of the initial phases of AD is lower than that of FDG-PET evaluation of the neuronal lesion, amyloid PET-based assessment of amyloid burden, or neuronal perfusion by means of perfusion single-photon emission computed tomography (SPECT) [10]. The introduction of FDG-PET into the clinical practice has gradually led to the replacement of perfusion SPECT, considered now to be of value in the new AD criteria when PET is not available [11]. Consequently, brain FDG-PET imaging is usually prescribed to patients with clinically well-characterized cognitive impairment but still with an uncertain origin despite having conducted standard complementary tests (structural neuroimaging, blood analysis and other tests). In this scenario, FDG-PET can help to rule out or confirm the clinical suspicion of AD, and to aid in the differential diagnosis between AD and other conditions associated with dementia (Fig. 1).

In this review, we aim to comment the recently published recommendations for the use of FDG-PET emerged from the EANM/EAN taskforce in the context of the clinical diagnostic guidelines currently available, and to conceptualize further based on the latest evidences published in the field of the differential diagnosis among the main forms of dementia, specifically AD, FTD, vascular dementia (VaD), and depressive pseudodementia.

Search strategies and results

The literature search performed for this review (last update on January 2020) included the databases PubMed (https://www.ncbi.nlm.nih.gov) PMC, Google Scholar, Medline using predefined keyword strings for each of the main topics covered. As FDG-PET was common to all topics, the following string was added at the end: AND ((("Positron emission tomography"[Title] OR "Cerebral positron emission tomography" [Title] OR "PET" [Title]) AND ("Fluorodeoxyglucose" [Title] OR "FDG"[Title] OR "glucose metabolism"[Title] OR "Cerebral metabolic rate of glucose"[Title] OR "Metabolism"[Title] OR "metabolic activity"[Title] OR "metabolic networks"[Title] OR "Hypometabolism"[Title])) OR ("FDG PET"[Title] OR "FDG-PET"[Title] OR "18F-FDG PET"[Title])) NOT review.

The resultant search was limited to the last 5 years, original articles, English language and humans. Finally, publications that were outside the focus of this review were also excluded.

For the MCI and AD we combined the following strings: ("MCI" OR "Mild cognitive impairment" OR "prodromal" OR conver*) AND "Alzheimer"). We found 48 publications, of which 13 papers were excluded. Nine were related to other conditions not covered in this review, three were methodological studies for imagine processing and one was a review article.

As for atypical AD (AD variants), we used the following strings: ("Alzheimer" OR "dementia") AND ("atypical"

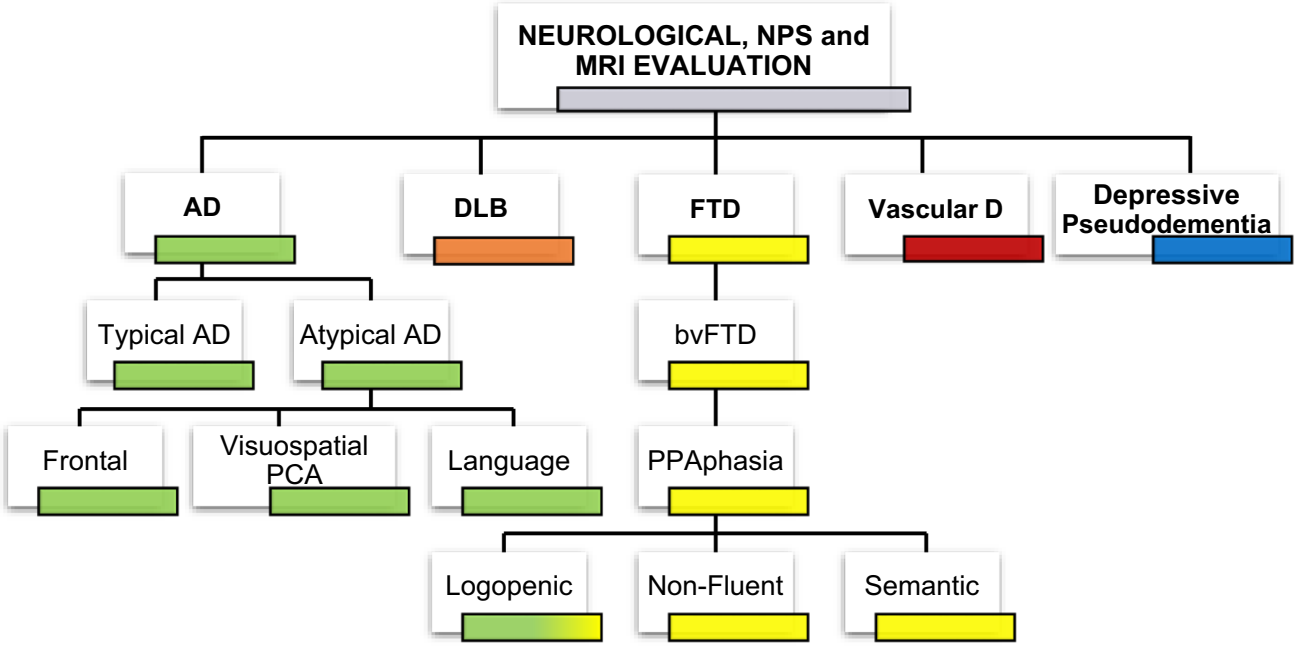

Fig. 1 Differential diagnosis among the main forms of dementia after neurological, neuropsychological assessment (NPS) and MRI evaluation. *AD* Alzheimer's disease; *DLB* Dementia with Lewy bodies; *FTD* Fronto-temporal dementia; *Vascular D* Vascular Dementia; *bvFTD* behavioural variant FTD; *PPAphasia* Primary Progressive Aphasia; *PCA* Posterior Cortical Atrophy

OR "focal" OR "posterior" OR "logopenic" OR "frontal variant"), obtaining a 40 publications. Nevertheless, we excluded 16 papers, because they were related to other conditions not covered in this review (10), include only technical issues (3), low number of subjects or related to other radiotracers (3).

We divided the searching for FTD in three blocks, one general and two specific for the differential diagnosis with AD, and the PPA. Initially, we used "FTD" OR "FTLD" OR "frontotemporal" OR "fronto-temporal" resulting in 37 publications, but only 4 included more than 15 subjects. Secondly, we used "Alzheimer" AND ("FTLD" OR "FTD" OR "frontotemporal" OR "fronto-temporal") AND "differential diagnosis", and found three publications but only one directly related to the pursued topic. Finally, when used "Primary progressive aphasia" AND ("logopenic" OR "progressive nonfluent aphasia" OR "progressive non-fluent aphasia" OR "semantic" OR "agrammatic") AND "differential diagnosis", no additional publications were found.

The search conducted for differential diagnosis between AD and vascular dementia consisted on "Alzheimer" AND ("Vascular" OR "subcortical" OR "small vessels disease") AND "differential diagnosis". We found five papers, but three were excluded because were reviews and one because only included amyloid PET.

Lastly, when including ("depression" AND neurodeg*) AND ("disease" OR "disorder")) OR ("pseudo-dementia" OR "depressive pseudo-dementia"), we did not find any additional publication during the last 5 years. Consequently, we tried a more general search including only "cognitive impairment" and "depression", resulting in three publications but we exclude one because it was related to Parkinson disease.

Differential diagnosis of mild cognitive impairment (MCI) and its association with Alzheimer disease (AD).

MCI is a syndrome defined by an objective cognitive decline according to the individual's age and educational background. Subjects with MCI are characterized by mild difficulties when performing complex tasks that they used to perform easily. Nevertheless, they do not show deterioration in daily living activities, although they sometimes require minimal aid or assistance [7].

Subjects with MCI can evolve over time in different ways: remain stable, progress to AD or other type of dementia, or even reverse to normality [12]. It is important to note that individuals with MCI can be classified into two categories: amnestic MCI (a-MCI) if performance on neuropsychological tests of episodic memory is poor, and non-amnestic MCI (na-MCI) if they have impairments in other cognitive domains different to memory (attention, executive function, language and visuospatial skill). In addition, there may be involvement of a single domain or several domains [13].

The National institute on Aging-Alzheimer's Association Workgroup (NIA-AA) proposed clinical diagnostic criteria for MCI due to AD, including biomarkers that provide greater diagnostic certainty [7]. FDG-PET form part of the group of neuronal injury imaging biomarkers. Impaired activity in AD is evident as reduced FDG-PET uptake predominantly in temporo-parietal association areas, including the precuneus and posterior cingulate [12, 14]. To date, most studies have investigated which pattern of MCI is related to a higher risk of progressing to dementia. Chételat G et al. [15] found that converters had a significantly lower FDG-PET uptake than non-converters in the right posterior association cortex, whereas the posterior cingulate gyrus afforded only marginal differentiation. Drzezga A, et al. [16], studied the relation between FDG-PET and APOE genotype to predict progression to dementia. Affected areas included brain regions typically involved in AD, such as bilateral para/hippocampal cortex, inferior prefrontal cortex, temporal cortex, inferior parietal cortex, and posterior cingulate cortex. They found that observer-independent evaluation of individual FDG-PET has a high predictive accuracy (90%) relating to the progression of MCI to AD within a 16-month observation period; however, the prognostic value of genetic assessment alone was demonstrated to be comparatively low (63%).

More recently, authors have developed FDG-PET score systems in combinations with other biomarkers and neuropsychological tests to predict the progression to dementia [14, 17–19] with a great variability of critical outcome measures. Nevertheless, these results reflect the extensive work that is on-going to compare and validate analytical tools for guiding interpretation of FDG-PET within the heterogeneous MCI population [20]. Garibotto V et al. evaluated the impact of education and occupation on brain glucose metabolism measured with FDG-PET in 72 subjects with a-MCI, 42 subjects with probable AD and 144 controls [21]. The analysis showed that subjects with amnestic MCI and probable AD with a higher education–occupation had, for a comparable cognitive impairment, a more severe brain metabolic reduction in posterior temporo-parietal association areas and posterior cingulate gyrus than the ones with lower education–occupation, these finding possibly reflecting a brain reserve mechanism in subjects with high education/occupation level. Moreover, they found that subjects with amnestic MCI converters to AD had a hypometabolism pattern that affects the posterior parietal cortex and precuneus, very similar to the typical pattern observed in subjects with AD. Pagani M et al. [22] in a group of 29 subject with MCI and 14 controls, evaluated the ability of FDG-PET to identify subgroups of subject with MCI who progress to dementia from those who remain stable using a base voxel comparison. When MCI subjects were compared to controls a hypometabolism that included the bilateral posterior cingulate cortex, the left parietal precuneus and left fusiform gyrus were found. In addition, a large hypometabolic region in the left medium and superior temporal gyri and inferior parietal lobule was observed when compared to MCI non-converters. However, no significant differences were found in the comparison between controls vs non-converters, neither in the comparison between converters and AD. Therefore, the pattern of hypometabolism that characterizes MCI due to AD mainly includes posterior cingulate and posterior temporo-parietal areas (Fig. 2).

Accordingly, experts agreed on recommendation of FDG-PET mainly based on its high negative predictive value (77–95%), as well as, its characteristic posterior hypometabolism pattern. The available formal evidence showed a large range of sensitivity (38–98%), specificity (41–97%) and accuracy (66–96.8%) values for the differentiation between MCI subjects who converted to AD and those who remain stable or converted to non-AD conditions [12]. Nevertheless, this large variability has some impact on the moderate assessment effect, and on the inconsistency effect.

Among the factors that can account for heterogeneity in the available literature, differences in methodological approaches and image analysis are consistently present in the evaluated studies. Visual read is the most frequent method for brain FDG-PET evaluation, but publications from the last 5 years advocate for a combination of visual qualitative and semiquantitative analyses with well-defined thresholds and scaling procedures [23–25]. In addition, machine learning methods have emerged as a new area of interest in medical image analysis. This tool can be applied to molecular imaging to obtain topographical patterns of the metabolic brain networks, which may be helpful to understand the pathophysiology of the cognitive dysfunction in MCI and AD [26–30]. Additional efforts have focused on development and validation of score based on metabolism FDG-PET imaging or in conjunction with other relevant biomarkers that allow to predict the progression of MCI to AD dementia [27, 31–34].

In a recent multicentre study conducted in 80 MCI subjects [35], the accuracy for the prediction of conversion to AD using FDG-PET and computer-assisted methods was AUC = 0.82 (95% C.I. 0.73–0.92, $p < 0.001$). Interestingly, when directly comparing the traditional visual rating and composite scores of computer-assisted analyses, Kang JM et al. [25] found a significant increase of the AUC from 0.67 to 0.79 predicting the conversion to AD in a group of 54 MCI patients.

Consequently, recent publications confirm the usefulness of FDG-PET in the clinical diagnosis of patients with MCI due to AD, and reinforce the use of computer-assisted methods to increase accuracy.

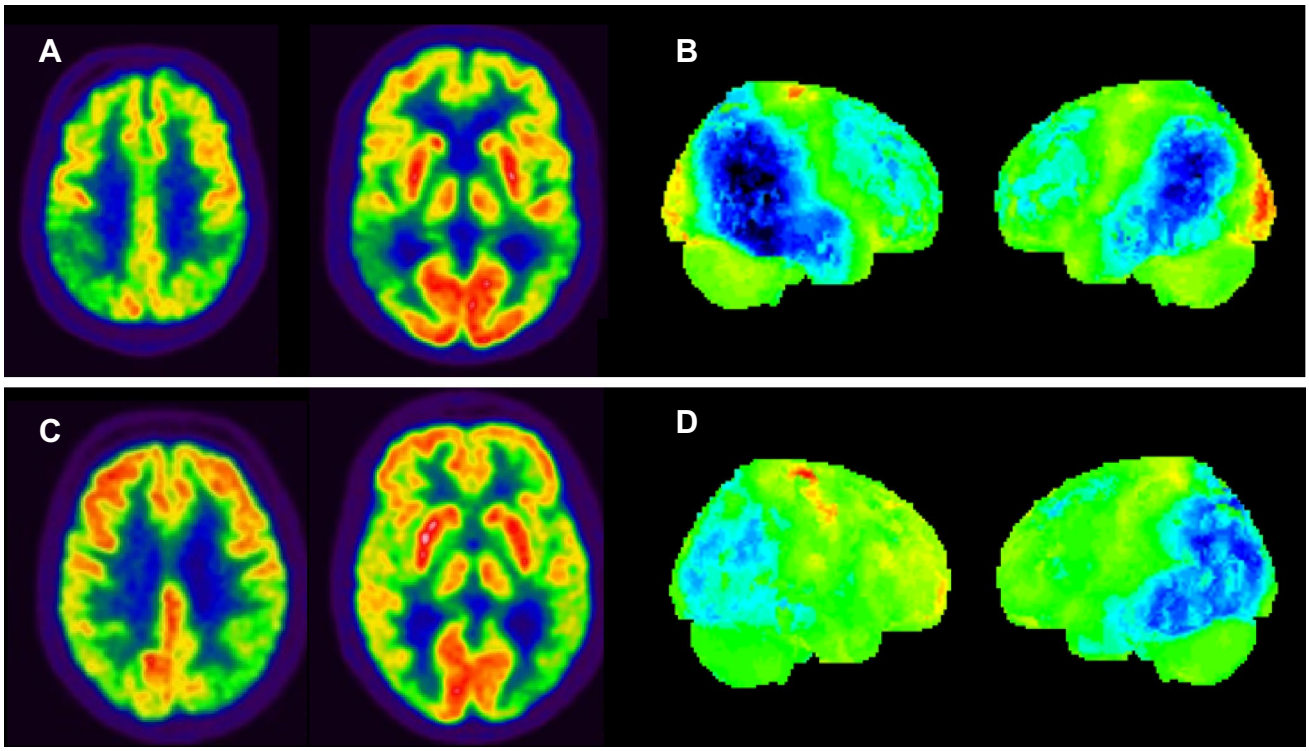

Fig. 2 Mild cognitive impairment due to Alzheimer's disease (AD). Examples of FDG-PET in two different patients with MCI due to AD. **a**, **c** Transaxial images **b**, **d** 3-dimensional stereotactic surface projection (3D-SSP) maps (Syngo via database comparison). *Upper panel,* 61-year-old patient with early-onset AD, with severe bilateral hypometabolism in temporo-parietal association areas and posterior cingulate, particularly on the right side. *Lower panel*, 67-year-old patient, late-onset AD with mild to moderate hypometabolism in temporo-parietal association areas and posterior cingulate on the left side. Both patients had a positive amyloid PET study, but hypometabolism is more marked in early-onset subject reflecting the effect of resilience and cognitive reserve

Atypical AD: patterns in AD variants

The typical presentation of AD dementia is a progressive memory impairment that eventually leads to a loss of functionality. However, about 6–14% of AD cases show atypical clinical presentations with visuospatial, language or behavioural/dysexecutive dominant symptoms, and are defined as visual, language and frontal variants of AD. These forms generally occur at an earlier age of onset than does typical amnestic AD and the memory domain is relatively preserved.[6, 20].

The **visual variant or posterior cortical atrophy (PCA)** was first introduced to describe patients with predominant deficits in higher order visual processing, a subset of whom also presented with marked atrophy in parieto-occipital areas [36]. Interestingly, AD is the most common underlying pathology in PCA. Some authors stablish subtypes into this category such as an occipito-temporal variant characterized by a predominant impairment in the visual identification of objects, symbols, words, or faces, and a biparietal variant with a predominant visuospatial dysfunction, features of Gerstmann, of Balint syndrome, limb apraxia, or neglect [20]. FDG-PET characteristically shows a predominant bilateral parieto-temporal hypometabolism pattern of AD but with additional involvement of the lateral occipital association cortices (Fig. 3) [37]. However, this occipital hypometabolism observed in PCA reminds the pattern shown in the dementia with Lewy bodies (DLB). In the study of Spehl et al., the discrimination accuracy of visual analysis and threshold selection of plotted regional FDG-PET uptake is compared between PCA and DLB [38]. They showed a specific area of hypometabolism in the right lateral temporo-occipital cortex related to PCA patients, while the hypometabolism predominantly in the left occipital cortex was related to DLB patients. The logistic regression based on these two regions correctly separated patients with PCA, DLB and AD with a sensitivity of 83%, specificity of 93% and accuracy of 91%. As highlighted by Nestor et al., additional areas like right posterior cingulate cortex/precuneus and right lateral parietal may also be affected in the PCA [39].

On the other hand, the language AD variant presents as **logopenic variant of primary progressive aphasia (lvPPA)**, is characterized by anomia, difficulty repeating complex sentences, and phonological errors [20, 40]. The hypometabolism pattern includes mainly left inferior frontal

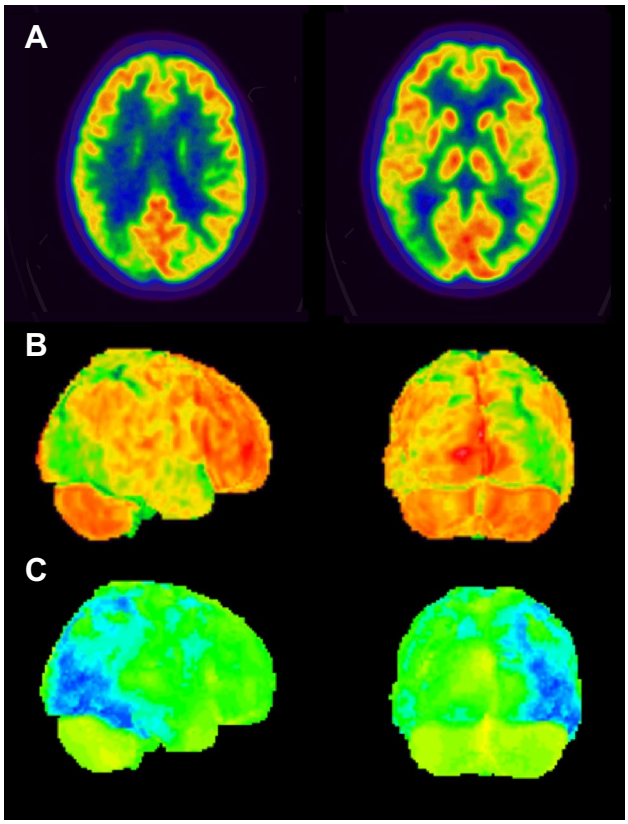

Fig. 3 Posterior Cortical Atrophy (PCA) in a 61-year-old patient. **a** Transaxial FDG-PET images **b** 3-dimensional stereotactic surface projection (3D-SSP) map of the patient **c** 3D-SSP map of the patient's uptake compared with a normality database (Syngo via database comparison). Reduced FDG uptake in posterior temporal cortex and in the occipito-temporal and parieto-occipital cortex on the right hemisphere is observed. The patient had a positive amyloid PET scan

and left temporo-parietal areas (see section on primary progressive aphasias) [41, 42].

In atypical AD, recent studies have shown a strong correlation between hypometabolism and tau deposition measured by [18F]AV-1451 PET [32]. PCA and lvPPA patients showed an increase of tau-PET tracer uptake in the parietal regions, more elevated in the occipital regions for PCA patients, and on the left side for lvPPA patients. These patterns of tau-PET mismatched the hypometabolism observed in FDG-PET, supporting the hypothesis that tau deposition has a close relationship to neurodegeneration and, therefore, it is likely a crucial player in determining regional patterns of hypometabolism [43].

In the case of **frontal variant of AD**, the clinical presentation is similar to behavioural variant of frontotemporal dementia (bvFTD), with progressive apathy or behavioural disinhibition and stereotyped behaviours, or with predominant executive dysfunction at testing. Although the visual and language variants are associated with AD pathology, only a few cases corresponds to the frontal variant with AD pathology in postmortem studies [20]. In such cases, the combination of FDG-PET and amyloid PET scanning might help distinguishing patients with frontal variant of AD from bvFTD, particularly on early onset [44]. Nevertheless, Woodward M. et al. evaluated 53 AD patients by means of frontal behavioural impairment assessment and PET-FDG, showing that medial-frontal and orbitofrontal hypometabolism was greater in AD patients presenting with more frontal/behavioural features [45].

A retrospective study examined the contribution of FDG-PET in the day-to-day diagnosis of dementia in a cohort of 94 patients (including 34 patients with atypical/unclear dementias). They found that FDG-PET was helpful in generating a more precise diagnosis in atypical/unclear cases, with a 59.5% of cases involved in a diagnostic change. In addition, the percentage of prescription of cholinesterase inhibitors before and after FDG PET imaging suggestive of AD increased significantly from 13.8 to 38.3% [37].

However, the formal evidence supporting the clinical utility of FDG-PET in the diagnosis of atypical presentation of AD from neurodegenerative diseases other than AD is still poor. The EANM and EAN consensual recommendation supports the use of FDG-PET, taking into account that, atypical AD may be difficult to detect at the individual level, where multiple biomarkers are often needed to reach a correct diagnosis, especially for clinicians with limited experience with these syndromes. The patterns of hypometabolism observed in FDG-PET may be useful to differentiate lvPPA from the remaining variants of PPA, and the visual variant of AD from DLB with typical cingulate island sign [41]. Furthermore, some national health services, social security or health insurances in European countries provide reimbursement of brain FDG-PET in unclear cases, unexplained dementia or atypical presentation [3].

Frontotemporal dementia

FTD is a macro-anatomical descriptive term for a clinically and pathologically heterogeneous group of disorders characterized collectively by a relatively selective progressive atrophy of the frontal and/or temporal lobes. Onset is typically in the sixth decade of life but may be as early as the third or as late as the ninth decade [46].

According to the EAN guidelines, most patients with FTD present with features conforming predominantly to behavioural variant (bvFTD) [46]. The language variants belong to different forms of aphasias who were classified by an international group of Primary Progressive Aphasias (PPA) in three variants: non-fluent/agrammatic (avPPA), semantic (svPPA), and logopenic (lvPPA) [8].

Clinical diagnosis of very early PPA or MCI stage of PPA is usually based on the presence of mild but persistent

isolated difficulty on tests of language (frequently dissociated from one patient to another), with relative preservation of other cognitive domains and activities of daily living [47]. Similar terms are adopted in bvFTD for patients with cognitive and/or behavioural impairment not fulfilling bvFTD criteria [9, 48]. A probable bvFTD must include frontal and/or temporal atrophy on MRI or CT, or hypoperfusion or hypometabolism on SPECT or PET [48]. In the multicentre study of Caminiti SP et al., FDG-PET using voxel-based analysis (SPM) was the most accurate biomarker (including CSF biomarkers) able to differentiate both the MCI subjects who converted to AD or FTD dementias, and those who remained stable or reverted to normal cognition, [35].

From the clinical point of view, bvFTD can be difficult to recognize, especially in the prodromal stage where behavioural changes may mimic psychiatric disorders and cognitive impairment is absent or subtle. A normal FDG PET scan is particularly valuable to exclude a neurodegenerative disease [4]. The addition of imaging criteria for the diagnosis of frontotemporal dementia improves specificity, particularly in those patients with behavioural symptoms [49]. The absence of brain atrophy in MRI is predictive of normal FDG metabolism in frontotemporal regions, irrespective of disease duration [49]**.** These different regional metabolic and structural heterogeneities, with temporal, orbitofrontal and medial prefrontal regions most affected; may explain key aspects of the clinical presentation [49–55].

FDG-PET hypometabolism in orbitofrontal or medial prefrontal regions and both anterior temporal lobe, are associated to bvFTD (Fig. 4). Studies using MRI with voxel-based morphometry (VBM) analyses and FDG PET in patients with probable bvFTD controlled with healthy subjects, show a significant diffuse frontotemporal grey matter volume reduction and hypometabolism, particularly medial prefrontal, orbital and insular and the anterior temporal lobes, with a relative sparing of the dorsolateral prefrontal cortex [9, 49]. Another VBM MRI study comparing 48 patients (25 avPPA with 23 bvFTD) controlled with 34 healthy subjects showed distinctive atrophy patterns affecting the left and right anterior insula regions respectively. Within the insula, avPPA patients showed greater atrophy in the left superior precentral region of the dorsal anterior insular, while bvFTD patients showed greater atrophy in bilateral ventral anterior insular atrophy [55]. The sensitivity of combined neuroimaging in bvFTD, MRI and additional FDG-PET together was 96% (95% CI 85–100%) and the specificity was 73% (95% CI 63–81%). The positive and negative predictive values of neuroimaging in a cohort with behavioural changes for bvFTD was 53% (95% CI 40–67%) and 98% (95% CI 93–100%), respectively [56].

In summary, FDG-PET may help an accurate clinical diagnosis of subjects with bvFTD, although the formal evidence to support the diagnosis of MCI due to FTD is still lacking. However, both the typical metabolic pattern in FTD that can be present at MCI stage, as well as the recently confirmed high negative predictive value further support the recommendation of using FDG-PET in the clinical diagnosis of FTD. Publications from the last 5 years also reveal different regional metabolic and structural heterogeneities in FTD, probably reflecting different clinical presentations.

Differentiating AD from FTD

Differentiating FTD from AD on clinical–neuropsychological grounds alone may sometimes be challenging, mostly in situations where reliable informant history is limited, or when symptoms are atypical [41]. Several studies using visual, voxel-based comparison and ROI analysis using FDG-PET demonstrated a 80–99% range sensitivity, a 63–98% specificity and accuracy from 87 to 89.2% [43, 46, 47], with a 98% positive predicted values, 74% negative predictive

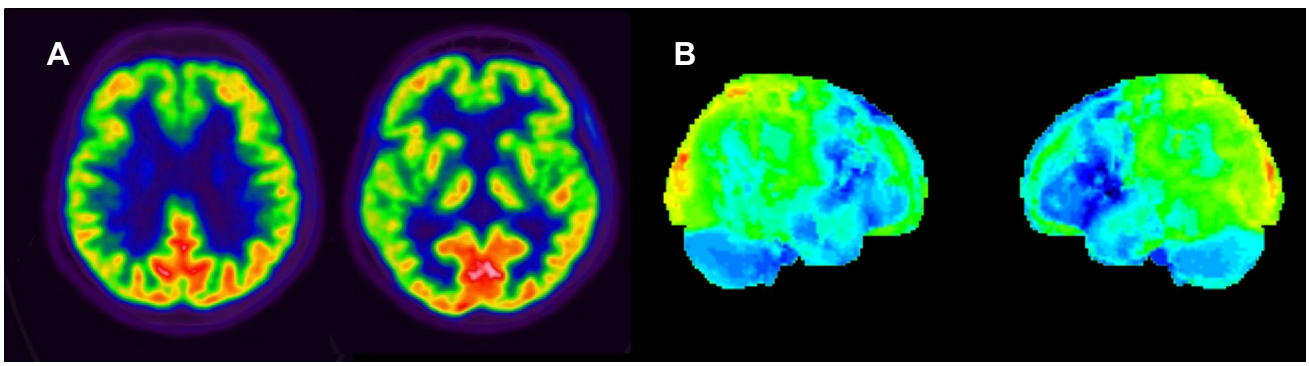

Fig. 4 Behavioural variant Fronto-temporal Dementia (bvFTD) in a 66-year-old female. **a** Transaxial FDG-PET images **b** 3D-SSP map of the patient's uptake compared with a normality database (Syngo via database comparison). Bilaterally reduced FDG uptake was observed in the dorsomedial and dorsolateral prefrontal cortex, mainly on the left side, as well as bilateral hypometabolism in the temporal pole, with normal parietal and posterior cingulate uptake. The patient had a negative amyloid PET scan

value, 29.88 positive likelihood ratio and 0.25 negative likelihood ratio [59].

In most cases, the hypometabolic patterns of FTD and AD are clearly separated, and consequently FDG-PET was included in the EANM/EAN clinical recommendations and covered by national health services or health insurances in different countries. The involvement of the prefrontal, insular and anterior cingulate cortex, basal ganglia, and sometimes with crossed cerebellar diaschisis is more frequently observed in FTD (particularly in bvFTD); and the posterior cingulate cortex and precuneus hypometabolism in AD [4].

Some degree of hypometabolism can, however, be found in parietal cortex in FTD patients, though this is characteristically less pronounced than the prefrontal lesion. Although posterior association cortex hypometabolism may occur in FTD and prefrontal hypometabolism occurs in AD, it has been recently detailed that the relative gradient—rostral worse than caudal in FTD and vice versa in AD—has discriminant value reinforcing the recommendation of FDG-PET use in the differential diagnosis between FDT and AD [42].

Table 1 Speech and language functions in PPA variants

Speech/language production	Nonfluent/ Agrammatic	Semantic	Logopenic
Grammar	YES	NO	NO
Motor speech	YES	NO	NO
Confrontation naming	NO	YES	YES
Repetition	NO	NO	YES
Sentence comprehension	YES	NO	YES
Single-word comprehension	NO	YES	NO
Object/people knowledge	NO	YES	NO
Reading/spelling	NO	YES	YES
	NO: spared	YES: impaired	

Adapted from M.L. Gorno-Tempini et al.[8]

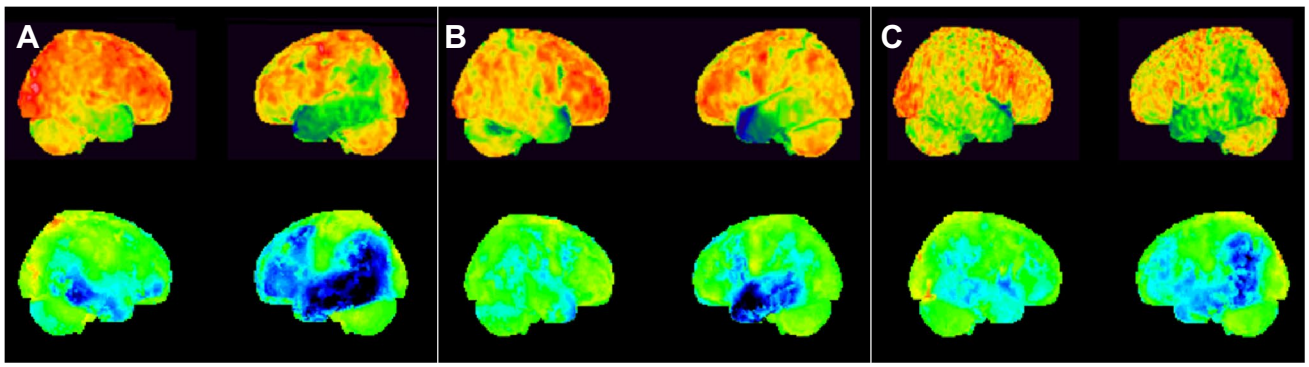

Fig. 5 The three variants of Primary Progressive Aphasias (PPA): **a** non-fluent/agrammatic (avPPA); **b** semantic (svPPA); and **c** logopenic (lvPPA). Examples of FDG-PET. *Upper panel,* 3-dimensional stereotactic surface projection (3D-SSP) map of each patient *Lower panel*, 3D-SSP map of patients' uptake compared with a normality database (Syngo via database comparison). **a** avPPA: predominant left posterior fronto-insular and anterior temporal hypometabolism; **b** svPPA: predominant left anterior temporal temporal hypometabolism, without hypometabolism of temporo-parietal association areas or posterior cingulate **c** lvPPA: predominant left posterior parieto-temporal hypometabolism, in this case with slight right temporal hypometabolism

Table 2 Correlation among clinical diagnosis of PPA variants and FDG PET

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Nonfluent/agrammatic	91.6	100	100	95.2
Semantic	60	100	100	93.1
Logopenic	91.6	33.3	86.2	66.6

Primary progressive aphasia

The three typical types of language variants of FTD are avPPA, svPPA and lvPPA. The main differences among these clinical variants are described in Table 1. The FDG-PET pattern associated to avPPA is a predominant left posterior fronto-insular hypometabolism; in svPPA there is an anterior temporal hypometabolism mostly bilateral, but predominantly left; and the lvPPA is associated to predominant left posterior perisilvian or parietal hypometabolism (Fig. 5) [8].

A study performed by Matias-Guiu et al. [60] found a good correlation between clinical diagnosis and FDG-PET findings with a 100% specificity for avPPA and svPPA, and 94.4% for lvPPA. The sensibility was 91.6%, 60% and 91.6%, respectively (Table 2).

In addition, Taswell et al. [61] showed an 84% accuracy, 85% sensitivity and 83% specificity for FDG-PET in predicting AD pathology using amyloid-PET. The accuracy, sensibility and specificity obtained by clinical evaluation was 65%, 41% and 93%, respectively; thus demonstrating that FDG-PET helps clinical diagnosis of patients with focal-onset variants of AD.

PPA variants diagnosis according to the current classification scheme is associated with biomarker status, [62, 63]. The logopenic variant is associated with amyloid-PET positivity in more than 95% of cases. The avPPA is commonly associated with FTD tau 4R (a pathological product seen in tauopathies), but also transactive response DNA-binding protein 43 (TDP-43) and progranulin mutations; less frequently, AD pathology has also been reported. A recent study investigating PPA patients with discordant amyloid status (i.e., avPPA with AD pathology) has suggested that most of these cases currently present mixed pathology (FTD tau pathology as primary pathologic diagnosis and AD pathology as contributing pathologic diagnosis). svPPA is nearly always associated with TDP-43 pathological aggregates and the remainder of patients most often have FTD tau, rarely AD pathology has been reported. The lvPPA is most often caused by AD pathology [63]. Interestingly, there are some patients who cannot be ascribed to the typical PPA classifications or they meet the criteria for more than one subtype, called unclassifiable/mixed PPA. For these patients, a variety of underlying diseases have been reported: FTLD

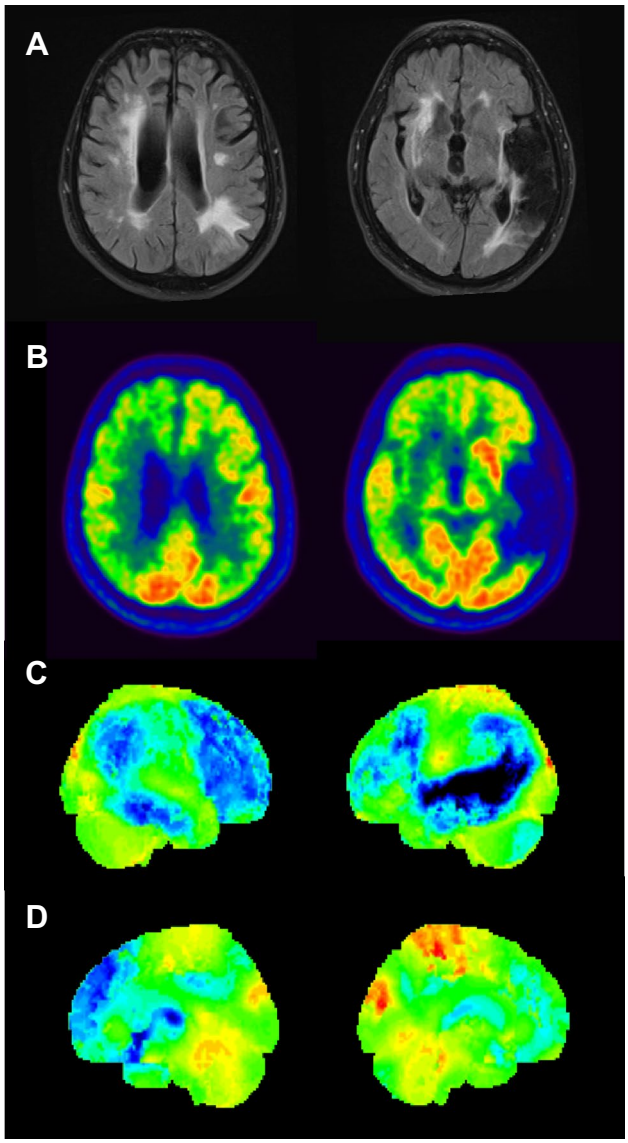

Fig. 6 Mixed vascular dementia and Alzheimer's disease (AD) in 77-year old patient. **a** Transaxial T2-weighted-Fluid-Attenuated Inversion Recovery (T2-FLAIR) of Magnetic Resonance Imaging (MRI). **b** Transaxial FDG-PET. **c** and **d** lateral and medial 3D-SSP map of the patient's uptake compared with a normal database (Syngo via database comparison). Temporo-parietal and frontal hypometabolism, predominantly on the right side suggested AD. However, ametabolic regions in the left temporal lobe and right subcortical were associated with previous atherotrobotic strokes in the left and right middle cerebral artery

tau (9.1%), TDP-43 (36.4%) and AD pathology (54.6%) [64].

In a recently published meta-analysis amyloid-β pathology was evaluated in 1251 patients with PPA (lvPPA, $n=443$; avPPA, $n=333$], svPPA, $n=401$, and unclassifiable $n=74$) [65]. They found that amyloid-β positivity increased with age in avPPA (from 10% at age 50 years to 27% at age 80 years, $p<0.01$) and svPPA (from 6% at age 50 years to 32% at age 80 years, $p<0.001$), but not in lvPPA ($p=0.94$) [65]. In this last case, the prevalence was 86%. Autopsy data revealed Alzheimer disease pathology as the most common pathologic diagnosis in lvPPA (76%), frontotemporal lobar degeneration–TDP-43 in svPPA (80%), and frontotemporal lobar degeneration–TDP-43/tau in nfvPPA (64%) [65].

A prospective clinico-pathological and amyloid PET study on 89 PPA patients (28 cases as svPPA, 31 avPPA, 26 lvPPA and 4 mixed/unclassified PPA cases), showed that 24 out of 28 patients with svPPA (86%) and 28 out of 31 patients with avPPA (90%) had negative amyloid PET scan results [62]. However, 25 out of 26 patients with lvPPA (96%) and 3 out of 4 mixed PPA cases (75%) had positive scan results [62]. The amyloid-positive svPPA and avPPA cases with available autopsy data (two out of four, and two out of three, respectively) all had a primary FTD and secondary AD pathologic diagnoses, whereas autopsy of two patients with amyloid PET-positive lvPPA confirmed Alzheimer disease. Furthermore, in the presence of a clinical syndrome highly predictive of FTD pathology, biomarker positivity for Alzheimer disease may be associated more with mixed pathology rather than primary AD.

Moreover, when evaluating amyloid deposit in lvPPA patients, a larger FDG hypometabolism in the left superior and medial temporal gyri, inferior parietal lobule, precuneus, angular and supramarginal gyrus is seen in amyloid-positive cases [66]. In contrast, amyloid-negative lvPPA patients displayed lower metabolism in the left superior, medial and inferior temporal gyri, left fusiform gyrus, uncus, left parietal lobe and supramarginal gyrus [66]. When comparing FDG metabolism between amyloid-positive and negative groups, metabolism was lower in the parietal lobules and right posterior cingulate in amyloid positive. On the other hand, amyloid-negative patients exhibited hypometabolism in the left anterior temporal and left frontal regions (inferior and middle frontal gyri, orbital gyri), and left temporal (superior and medial temporal gyri) [66]. These results reinforced the role of FDG-PET in the differential diagnosis of PPA and AD.

Recently, the use of an automated algorithm based on regional brain metabolism by FDG-PET demonstrated the existence of five subtypes of PPA in early stages (avPPA type 1 and 2, lvPPA type 1 and 2 and svPPA) [59]. The first avPPA showed involvement of the left frontal lobe (Broca's area, but also the anterior cingulate and superior and middle frontal gyri), extending to other regions of the left hemisphere. In contrast, the second variant (k2) also involved the inferior frontal gyrus but tended to affect more medial regions, as well as the right frontal lobe. The logopenic type 1 were women, while all patients with logopenic type 2 were men. Both types involve the left parieto-temporal junction, but type 1 tends to extend to the left frontal lobe, whereas type 2 involves a more posterior region and the right parieto-temporal lobe [67, 68].

Although EANM/EAN panel evidenced a lack of formal evidence of FDG-PET for assessing the differential diagnosis between several forms of PPA, they recommended it use based on the specificity of typical patterns of hypometabolism, and this biomarker is definitively included in the current clinical diagnostic criteria. These findings are an early phenomenon in PPA and consequently FDG-PET can be more sensitive than MRI, although they both form part of the current clinical diagnostic criteria of PPA [69]. Despite the lack of additional formal evidence, the recent literature has provided additional bases and further knowledge that emphasize the use of FDG-PET in these conditions.

Vascular dementia

Vascular dementia (VaD) is the second most common cause of dementia after AD [70]. Individuals at the highest risk for VaD are those with a recent history of stroke or transient ischemic attacks [71]. Cognitive deficits in VaD are much more variable than in other disorders such AD, and are highly dependent on the particular neural substrates affected by the vascular pathology [72]. Many cases of dementia have been reported to display both AD and VaD traits, and over 80% of AD necropsies show evidence of cerebrovascular disease [73]. It is difficult to establish the relative weight of the two components in causing the clinical dementia. The existing literature in this field is particularly limited, as we lack studies with pathological diagnosis as the reference standard [41].

When high number of cerebrovascular lesions are identified during initial testing, vascular ischaemia becomes the main determining factor for diagnosing a patient with vascular mild cognitive impairment (vMCI) [74].

Different patterns of hypometabolism in FDG-PET have been described associated with vascular cognitive impairment. In the study of Seo et al., subjects with vMCI showed more severe hypometabolism in the thalamus, brainstem and cerebellum, as opposed to amnestic MCI who showed hypometabolism in the posterior cingulate and temporo-parietal cortex [75]. When patients with vascular disease with and without dementia are compared with normal controls, those with vascular dementia (VaD) show a decreased metabolism

in both frontal lobes and right supramarginal gyrus, but not in the precuneus or temporal lobes. Patients with vascular disease without dementia, also show a less significant hypometabolism in the same regions to those patients with VaD. A direct comparison between the two groups of vascular patients showed that dementia was associated with larger hypometabolism in the frontal lobes [76].

Kerrouche et al. applied a voxel-based multivariate analysis in their study to evaluate the accuracy of FDG-PET in differentiating between VaD and AD patients using canonical variate analysis. This method extracted a hypometabolic pattern that efficiently differentiated VaD (frontal, anterior cingulate, temporal, and occipital cortex, basal ganglia and thalamus) and AD (posterior cingulate and parietal cortex) with 100% accuracy (Fig. 6). Moreover, this methodology was able to separate as a group, normal controls from demented subjects with a sensitivity and specificity of 72% and 96% respectively [77].

In the EANM/EAN consensual recommendations, the use of FDG-PET is supported in patients with vascular pathology only based in the identification of AD when the characteristic AD pattern of bilateral posterior temporo-parietal hypometabolism can be seen, if these hypometabolic regions are not co-localised with cortical infarcts on structural scans [41]. At this respect, it is important to note that FDG-PET should be reported after reviewing or fusing with the structural imaging; although this is a generally recommended clinical practice when degenerative brain disease is suspected [41]. Unfortunately, during the last 5 years, there are not additional formal evidences in the literature for the differential diagnosis between AD and VaD supporting a characteristic pattern for this last condition. However, FDG-PET is being applied as part of the clinical practice supporting the clinical diagnosis of AD, MCI or VaD as demonstrated in a recently published conducted in a cohort of 68 patients [78].

Depressive pseudodementia

Elderly depressive patients complaining about cognitive symptoms are at particular risk of being labelled as demented. It is well documented that depressive disorders frequently cause mild cognitive deficits which manifest in psychometric procedures [79]. Depressive pseudodementia is a relatively uncommon problem, but it is critical not to miss it because of its potential reversibility [29]. The term has been used to describe the cognitive profile of various psychiatric disorders, especially depression in old age, which present with cognitive deterioration in dementia [80].

A study that combined FDG-PET and fMRI in resting cerebral function in patients with major depressive disorder and healthy controls showed decreased glucose uptake in the bilateral superior, the middle and the inferior frontal gyrus, in the bilateral superior and middle temporal gyrus, in the bilateral anterior cingulate cortex, in the bilateral putamen and caudate, and in the left globus pallidus, but an increased glucose uptake in the bilateral hippocampus and left thalamus, with no statistically significant differences between PET and fMRI [81]. HS Lee et al. evaluated patients with MCI with depression (MCI-D), and compared to MCI with no depression (MCI-ND) and healthy controls. They found more severe hypometabolism in right superior frontal gyrus in MCI-D than MCI-ND, and a significant negative correlation between Hamilton Rating Scale for Depression and glucose metabolism in the right superior frontal gyrus in overall MCI subjects [82].

In a recently published study, 31 patients with MCI and concomitant depression were evaluated according to the result of the amyloid PET scan [83]. Interestingly, MCI patients with depression and amyloid positive showed a reduced regional cerebral glucose metabolism in temporo-parietal regions when comparing to age adjusted normal controls. On the other hand, the amyloid-negative group not only exhibited lower metabolism in temporal regions but also showed involvement of orbitofrontal regions. The metabolism in the left inferior orbitofrontal region and the right anterior cingulate was significantly lower in the amyloid-negative group when a direct comparison between these two MCI groups with depression was conducted [83].

Nestor et al. recommend that the use of FDG-PET in the evaluation of depressive pseudodementia should be based on the knowledge that metabolic abnormalities are a function disease severity [41]. Thus, a clearly demented patient should always show obvious abnormalities on FDG-PET. Consequently, a normal FDG-PET scan offers strong evidence supporting pseudodementia, while a typical pattern of hypometabolism for one of the degenerative dementias argues against pseudodementia (high negative predictive value). It must be stressed that this recommendation specifically applies to patients with an apparent overt dementia on cognitive testing, and not to the more common and challenging situation of deciding whether patients with very mild or even subjective cognitive deficits have a primary psychiatric diagnosis versus the first signs of a degenerative disease.

Conclusions

FDG-PET is the most available PET radiotracer worldwide and it is being applied as part of the clinical practice supporting the clinical diagnosis of AD (at both MCI and early dementia stages), FTD, PPA, as well as VaD and pseudodepressive dementia. The pattern of AD is well defined and its negative predicted values may help the differential diagnosis when comorbidities like vascular disease or depression are present. However, the formal evidence supporting the use of FDG

is reasonable for MCI due to AD, and the differential diagnosis between FTD and AD, but lacking for the remaining clinical uses. Nevertheless, clinical diagnostic criteria include FDG-PET as a biomarker that helps the classification of subjects within PPA and different neuropathology. Interestingly, the evidence provided during the last years reinforces these recommendations and gives additional clues about the usefulness of computer-assisted methods (comparison with a normal database on a voxel by voxel bases) in addition to visual reading.

Conflict of interest

JA received research funding from Eli-Lilly, Piramal and GE Healthcare, and speaker honoraria from GE Healthcare, AAA, and Eisai. The remainder authors declare no conflict of interest.

Author contributions EFG, DL, JJR and JA: literature search and review. All authors: manuscript writing and editing.

Funding This study was not funded by grants.

Compliance with ethical standards

Ethical standards This article does not contain any studies with human or animal subjects performed by the any of the authors.

References

1. Jack CR, Knopman DS, Jagust WJ et al (2013) Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol 12:207–216. https://doi.org/10.1016/S1474-4422(12)70291-0
2. Lundgaard I, Li B, Xie L et al (2015) Direct neuronal glucose uptake heralds activity-dependent increases in cerebral metabolism. Nat Commun 6:6807. https://doi.org/10.1038/ncomms7807
3. Frisoni GB, Boccardi M, Barkhof F et al (2017) Strategic roadmap for an early diagnosis of Alzheimer's disease based on biomarkers. Lancet Neurol 16:661–676. https://doi.org/10.1016/S1474-4422(17)30159-X
4. Nobili F, Arbizu J, Bouwman F et al (2018) European association of nuclear medicine and European academy of neurology recommendations for the use of brain 18 F-fluorodeoxyglucose positron emission tomography in neurodegenerative cognitive impairment and dementia: Delphi consensus. Eur J Neurol 25:1201–1217. https://doi.org/10.1111/ene.13728
5. McKhann GM, Knopman DS, Chertkow H et al (2011) 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. Alzheimer's Dement 7:263–269. https://doi.org/10.1016/j.jalz.2011.03.005
6. Dubois B, Feldman HH, Jacova C et al (2014) Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 13:614–629. https://doi.org/10.1016/S1474-4422(14)70090-0
7. Albert MS, DeKosky ST, Dickson D et al (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the national Institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement 7:270–279. https://doi.org/10.1016/j.jalz.2011.03.008
8. Gorno-Tempini ML, Hillis AE, Weintraub S et al (2011) Classification of primary progressive aphasia and its variants. Neurology 76:1006–1014. https://doi.org/10.1212/WNL.0b013e31821103e6
9. Borroni B, Cosseddu M, Pilotto A et al (2015) Early stage of behavioral variant frontotemporal dementia: clinical and neuroimaging correlates. Neurobiol Aging 36:3108–3115. https://doi.org/10.1016/j.neurobiolaging.2015.07.019
10. Yuan Y, Gu ZX, Wei WS (2009) Fluorodeoxyglucose-positron-emission tomography, single-photon emission tomography, and structural MR imaging for prediction of rapid conversion to alzheimer disease in patients with mild cognitive impairment: a meta-analysis. Am J Neuroradiol 30:404–410. https://doi.org/10.3174/ajnr.A1357
11. Frisoni GB, Bocchetta M, Chételat G et al (2013) Imaging markers for Alzheimer disease: Which vs how. Neurology 81:487–500
12. Arbizu J, Festari C, Altomare D et al (2018) Clinical utility of FDG-PET for the clinical diagnosis in MCI. Eur J Nucl Med Mol Imaging 45:1497–1508. https://doi.org/10.1007/s00259-018-4039-7
13. Winblad B, Palmer K, Kivipelto M, et al (2004) Mild cognitive impairment—beyond controversies, towards a consensus: report of the international working group on mild cognitive impairment. En: Journal of Internal Medicine. Wiley, pp 240–246
14. Herholz K, Westwood S, Haense C, Dunn G (2011) Evaluation of a calibrated (18)F-FDG PET score as a biomarker for progression in Alzheimer disease and mild cognitive impairment. J Nucl Med 52:1218–1226. https://doi.org/10.2967/jnumed.111.090902
15. Chételat G, Desgranges B, de la Sayette V et al (2003) Mild cognitive impairment: Can FDG-PET predict who is to rapidly convert to Alzheimer's disease? Neurology 60:1374–1377. https://doi.org/10.1212/01.wnl.0000055847.17752.e6
16. Drzezga A, Grimmer T, Riemenschneider M et al (2005) Prediction of individual clinical outcome in MCI by means of genetic assessment and 18F-FDG PET. J Nucl Med 46:1625–1632
17. Arbizu J, Prieto E, Martínez-Lage P et al (2013) Automated analysis of FDG PET as a tool for single-subject probabilistic prediction and detection of Alzheimer's disease dementia. Eur J Nucl Med Mol Imaging 40:1394–1405. https://doi.org/10.1007/s00259-013-2458-z
18. Young J, Modat M, Cardoso MJ et al (2013) Accurate multimodal probabilistic prediction of conversion to Alzheimer's disease in patients with mild cognitive impairment. NeuroImage Clin 2:735–745. https://doi.org/10.1016/j.nicl.2013.05.004
19. Ito K, Fukuyama H, Senda M et al (2015) Prediction of outcomes in mild cognitive impairment by Using 18F-FDG-PET: a multicenter study. J Alzheimer's Dis 45:543–552. https://doi.org/10.3233/JAD-141338
20. Dubois B, Feldman HH, Jacova C et al (2010) Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol 9:1118–1127. https://doi.org/10.1016/S1474-4422(10)70223-4
21. Garibotto V, Borroni B, Kalbe E et al (2008) Education and occupation as proxies for reserve in aMCI converters and AD: FDG-PET evidence. Neurology 71:1342–1349. https://doi.org/10.1212/01.wnl.0000327670.62378.c0
22. Pagani M, Dessi B, Morbelli S et al (2010) MCI Patients declining and not-declining at mid-term follow-up: FDG-PET findings. Curr

Alzheimer Res 7:287–294. https://doi.org/10.2174/156720510791162368
23. Grimmer T, Wutz C, Alexopoulos P et al (2016) Visual versus fully automated analyses of 18F-FDG and amyloid PET for prediction of dementia due to Alzheimer disease in mild cognitive impairment. J Nucl Med 57:204–207. https://doi.org/10.2967/jnumed.115.163717
24. Kim J, Cho S-G, Song M et al (2016) Usefulness of 3-dimensional stereotactic surface projection FDG PET images for the diagnosis of dementia. Medicine (Baltimore) 95:e5622. https://doi.org/10.1097/MD.0000000000005622
25. Kang JM, Lee JY, Kim YK et al (2018) Visual rating and computer-assisted analysis of FDG PET in the prediction of conversion to alzheimer's disease in mild cognitive impairment. Mol Diagnosis Ther 22:475–483. https://doi.org/10.1007/s40291-018-0334-z
26. Kuang L, Zhao D, Xing J et al (2019) Metabolic Brain network analysis of FDG-PET in alzheimer's disease using kernel-based persistent features. Molecules 24:2301. https://doi.org/10.3390/molecules24122301
27. Popuri K, Balachandar R, Alpert K et al (2018) Development and validation of a novel dementia of Alzheimer's type (DAT) score based on metabolism FDG-PET imaging. NeuroImage Clin 18:802–813. https://doi.org/10.1016/j.nicl.2018.03.007
28. Yao Z, Hu B, Chen X et al (2018) Learning metabolic brain networks in MCI and AD by robustness and leave-one-out analysis: an FDG-PET study. Am J Alzheimers Dis Other Demen 33:42–54. https://doi.org/10.1177/1533317517731535
29. Pagani M, Giuliani A, Öberg J et al (2017) Progressive disintegration of brain networking from normal aging to alzheimer disease: analysis of independent components of ^{18} F-FDG PET data. J Nucl Med 58:1132–1139. https://doi.org/10.2967/jnumed.116.184309
30. Didic M, Felician O, Gour N et al (2015) Rhinal hypometabolism on FDG PET in healthy APO-E4 carriers: impact on memory function and metabolic networks. Eur J Nucl Med Mol Imaging 42:1512–1521. https://doi.org/10.1007/s00259-015-3057-y
31. Ottoy J, Niemantsverdriet E, Verhaeghe J et al (2019) Association of short-term cognitive decline and MCI-to-AD dementia conversion with CSF, MRI, amyloid- and 18F-FDG-PET imaging. NeuroImage Clin 22:101771. https://doi.org/10.1016/j.nicl.2019.101771
32. Riederer I, Bohn KP, Preibisch C et al (2018) Alzheimer disease and mild cognitive impairment: integrated pulsed arterial spin-labeling MRI and 18F-FDG PET. Radiology 288:198–206. https://doi.org/10.1148/radiol.2018170575
33. Stonnington CM, Chen Y, Savage CR et al (2018) Predicting imminent progression to clinically significant memory decline using volumetric MRI and FDG PET. J Alzheimers Dis 63:603–615. https://doi.org/10.3233/JAD-170852
34. Lange C, Suppa P, Frings L et al (2016) Optimization of statistical single subject analysis of brain FDG PET for the prognosis of mild cognitive impairment-to-alzheimer's disease conversion. J Alzheimers Dis 49:945–959. https://doi.org/10.3233/JAD-150814
35. Caminiti SP, Ballarini T, Sala A et al (2018) FDG-PET and CSF biomarker accuracy in prediction of conversion to different dementias in a large multicentre MCI cohort. NeuroImage Clin 18:167–177. https://doi.org/10.1016/j.nicl.2018.01.019
36. Crutch SJ, Lehmann M, Schott JM et al (2012) Posterior cortical atrophy. Lancet Neurol 11:170–178
37. Laforce R, Buteau JP, Paquet N et al (2010) The value of PET in mild cognitive impairment, typical and atypical/unclear dementias: a retrospective memory clinic study. Am J Alzheimers Dis Other Demen 25:324–332. https://doi.org/10.1177/1533317510363468
38. Spehl TS, Hellwig S, Amtage F et al (2015) Syndrome-specific patterns of regional cerebral glucose metabolism in posterior cortical atrophy in comparison to dementia with Lewy bodies and Alzheimer's disease–a [F-18]-FDG pet study. J Neuroimaging 25:281–288. https://doi.org/10.1111/jon.12104
39. Nestor PJ, Caine D, Fryer TD et al (2003) The topography of metabolic deficits in posterior cortical atrophy (the visual variant of Alzheimer's disease) with FDG-PET. J Neurol Neurosurg Psychiatry 74:1521–1529. https://doi.org/10.1136/jnnp.74.11.1521
40. Whitwell JL, Duffy JR, Strand EA et al (2015) Clinical and neuroimaging biomarkers of amyloid-negative logopenic primary progressive aphasia. Brain Lang 142:45–53. https://doi.org/10.1016/j.bandl.2015.01.009
41. Nestor PJ, Altomare D, Festari C et al (2018) Clinical utility of FDG-PET for the differential diagnosis among the main forms of dementia. Eur J Nucl Med Mol Imaging 45:1509–1525. https://doi.org/10.1007/s00259-018-4035-y
42. Laforce R, Tosun D, Ghosh P et al (2014) Parallel ICA of FDG-PET and PiB-PET in three conditions with underlying Alzheimer's pathology. NeuroImage Clin 4:508–516. https://doi.org/10.1016/j.nicl.2014.03.005
43. Sintini I, Schwarz CG, Martin PR et al (2019) Regional multimodal relationships between tau, hypometabolism, atrophy, and fractional anisotropy in atypical Alzheimer's disease. Hum Brain Mapp 40:1618–1631. https://doi.org/10.1002/hbm.24473
44. Ossenkoppele R, Prins ND, Pijnenburg YAL et al (2013) Impact of molecular imaging on the diagnostic process in a memory clinic. Alzheimer's Dement 9:414–421. https://doi.org/10.1016/j.jalz.2012.07.003
45. Woodward MC, Rowe CC, Jones G et al (2015) Differentiating the frontal presentation of Alzheimer's disease with FDG-PET. J Alzheimer's Dis 44:233–242. https://doi.org/10.3233/JAD-141110
46. Sorbi S, Hort J, Erkinjuntti T et al (2012) EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia. Eur J Neurol 19:1159–1179. https://doi.org/10.1111/j.1468-1331.2012.03784.x
47. Rogalski E, Mesulam M (2009) Clinical trajectories and biological features of primary progressive aphasia (PPA). Curr Alzheimer Res 6:331–336. https://doi.org/10.2174/156720509788929264
48. Rascovsky K, Hodges JR, Knopman D et al (2011) Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 134:2456–2477. https://doi.org/10.1093/brain/awr179
49. Kipps CM, Hodges JR, Fryer TD, Nestor PJ (2009) Combined magnetic resonance imaging and positron emission tomography brain imaging in behavioural variant frontotemporal degeneration: Refining the clinical phenotype. Brain 132:2566–2578. https://doi.org/10.1093/brain/awp077
50. Devenney E, Bartley L, Hoon C et al (2015) Progression in behavioral variant frontotemporal dementia: A longitudinal study. JAMA Neurol 72:1501–1509. https://doi.org/10.1001/jamaneurol.2015.2061
51. Ranasinghe KG, Rankin KP, Pressman PS et al (2016) Distinct subtypes of Bvftd based on patterns of network degeneration. JAMA Neurology 73:1078–1088. https://doi.org/10.1001/jamaneurol.2016.2016.Distinct
52. Cerami C, Dodich A, Lettieri G et al (2016) Different FDG-PET metabolic patterns at single-subject level in the behavioral variant of fronto-temporal dementia. Cortex 83:101–112. https://doi.org/10.1016/j.cortex.2016.07.008
53. Fernández-Matarrubia M, Matías-Guiu JA, Cabrera-Martín MN et al (2017) Episodic memory dysfunction in behavioral variant frontotemporal dementia: a clinical and FDG-PET study. J Alzheimer's Dis 57:1251–1264. https://doi.org/10.3233/JAD-160874

54. Devenney E, Swinn T, Mioshi E et al (2018) The behavioural variant frontotemporal dementia phenocopy syndrome is a distinct entity—evidence from a longitudinal study. BMC Neurol 18:1–6. https://doi.org/10.1186/s12883-018-1060-1
55. Mandelli ML, Vitali P, Santos M, Henry M, Gola K, Rosenberg L, Dronkers N, Miller B, Seeley WW, Gorno-Tempini ML (2016) Two insular regions are differentially involved in behavioral variant FTD and nonfluent/agrammatic variant PPA. Cortex 74:149–157. https://doi.org/10.1016/j.cortex.2015.10.012
56. Vijverberg EGB, Wattjes MP, Dols A et al (2016) Diagnostic accuracy of MRI and additional [18F]FDG-PET for behavioral variant frontotemporal dementia in patients with late onset behavioral changes. J Alzheimer's Dis 53:1287–1297. https://doi.org/10.3233/JAD-160285
57. Mosconi L, Tsui WH, Herholz K et al (2008) Multicenter standardized 18F-FDG PET diagnosis of mild cognitive impairment, Alzheimer's disease, and other dementias. J Nucl Med 49:390–398. https://doi.org/10.2967/jnumed.107.045385
58. Foster NL, Heidebrink JL, Clark CM et al (2007) FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. Brain 130:2616–2635. https://doi.org/10.1093/brain/awm177
59. Rabinovici GD, Rosen HJ, Alkalay A et al (2011) Amyloid vs FDG-PET in the differential diagnosis of AD and FTLD. Neurology 77:2034–2042. https://doi.org/10.1212/WNL.0b013e31823b9c5e
60. Matias-Guiu JA, Cabrera-Martín MN, García-Ramos R et al (2014) Evaluation of the new consensus criteria for the diagnosis of primary progressive aphasia using fluorodeoxyglucose positron emission tomography. Dement Geriatr Cogn Disord 38:147–152. https://doi.org/10.1159/000358233
61. Taswell C, Villemagne VL, Yates P et al (2015) 18F-FDG PET improves diagnosis in patients with focal-onset dementias. J Nucl Med 56:1547–1553. https://doi.org/10.2967/jnumed.115.161067
62. Santos-Santos MA, Rabinovici GD, Iaccarino L et al (2018) Rates of amyloid imaging positivity in patients with primary progressive aphasia. JAMA Neurol 75:342–352. https://doi.org/10.1001/jamaneurol.2017.4309
63. Montembeault M, Brambati SM, Gorno-Tempini ML, Migliaccio R (2018) Clinical, anatomical, and pathological features in the three variants of primary progressive aphasia: a review. Front Neurol 9:692. https://doi.org/10.3389/fneur.2018.00692
64. Harris JM, Jones M (2014) Pathology in primary progressive aphasia syndromes. Curr Neurol Neurosci Rep 14:466. https://doi.org/10.1007/s11910-014-0466-4
65. Bergeron D, Gorno-Tempini ML, Rabinovici GD et al (2018) Prevalence of amyloid-β pathology in distinct variants of primary progressive aphasia. Ann Neurol 84:729–740. https://doi.org/10.1002/ana.25333
66. Matías-Guiu JA, Cabrera-Martín MN, Moreno-Ramos T et al (2015) Amyloid and FDG-PET study of logopenic primary progressive aphasia: evidence for the existence of two subtypes. J Neurol 262:1463–1472. https://doi.org/10.1007/s00415-015-7738-z
67. Matias-Guiu JA, Díaz-Álvarez J, Cuetos F et al (2019) Machine learning in the clinical and language characterisation of primary progressive aphasia variants. Cortex 119:312–323. https://doi.org/10.1016/j.cortex.2019.05.007
68. Matias-Guiu JA, Díaz-Álvarez J, Ayala JL et al (2018) Clustering analysis of FDG-PET imaging in primary progressive aphasia. Front Aging Neurosci 10:1–12. https://doi.org/10.3389/fnagi.2018.00230
69. Bouwman F, Orini S, Gandolfo F et al (2018) Diagnostic utility of FDG-PET in the differential diagnosis between different forms of primary progressive aphasia. Eur J Nucl Med Mol Imaging 45:1526–1533. https://doi.org/10.1007/s00259-018-4034-z
70. Jorm AF, Jolley D (1998) The incidence of dementia: a meta-analysis. Neurology 51:728–733. https://doi.org/10.1212/WNL.51.3.728
71. Gorelick PB (2004) Risk factors for vascular dementia and Alzheimer disease. Stroke 35:2620–2622. https://doi.org/10.1161/01.STR.0000143318.70292.47
72. O'Brien JT, Thomas A (2015) Vascular dementia. Lancet 386:1698–1706. https://doi.org/10.1016/S0140-6736(15)00463-8
73. Toledo JB, Arnold SE, Raible K et al (2013) Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the national alzheimer's coordinating centre. Brain 136:2697–2706. https://doi.org/10.1093/brain/awt188
74. MacLin JMA, Wang T, Xiao S (2019) Biomarkers for the diagnosis of Alzheimer's disease, dementia Lewy body, frontotemporal dementia and vascular dementia. Gen Psychiatry 32:5–13. https://doi.org/10.1136/gpsych-2019-100054
75. Seo SW, Cho SS, Park A et al (2009) Subcortical vascular versus amnestic mild cognitive impairment: comparison of cerebral glucose metabolism. J Neuroimaging 19:213–219. https://doi.org/10.1111/j.1552-6569.2008.00292.x
76. Pascual B, Prieto E, Arbizu J et al (2010) Brain glucose metabolism in vascular white matter disease with dementia: differentiation from Alzheimer disease. Stroke 41:2889–2893. https://doi.org/10.1161/STROKEAHA.110.591552
77. Kerrouche N, Herholz K, Mielke R et al (2006) 18FDG PET in vascular dementia: differentiation from Alzheimer's disease using voxel-based multivariate analysis. J Cereb Blood Flow Metab 26:1213–1221. https://doi.org/10.1038/sj.jcbfm.9600296
78. Vishnu VY, Modi M, Garg VK et al (2017) Role of inflammatory and hemostatic biomarkers in Alzheimer's and vascular dementia—a pilot study from a tertiary center in Northern India. Asian J Psychiatr 29:59–62. https://doi.org/10.1016/j.ajp.2017.04.015
79. Djukic M, Wedekind D, Franz A et al (2015) Frequency of dementia syndromes with a potentially treatable cause in geriatric in-patients: analysis of a 1-year interval. Eur Arch Psychiatry Clin Neurosci 265:429–438. https://doi.org/10.1007/s00406-015-0583-3
80. Kang H, Zhao F, You L, Giorgetta C, Sarkhel SPR (2014) Pseudodementia: a neuropsychological review. Ann Indian Acad Neurol 17:147–154. https://doi.org/10.4103/0972-2327.132613
81. Fu C, Zhang H, Xuan A et al (2018) A combined study of 18F-FDG PET-CT and fMRI for assessing resting cerebral function in patients with major depressive disorder. Exp Ther Med 16:1873–1881. https://doi.org/10.3892/etm.2018.6434
82. Lee HS, Il CH, Lee DY et al (2010) Frontal dysfunction underlies depression in mild cognitive impairment: a FDG-PET study. Psychiatry Investig 7:208–214. https://doi.org/10.4306/pi.2010.7.3.208
83. Youn HC, Lee ES, Lee S et al (2018) Regional glucose metabolism due to the presence of cerebral amyloidopathy in older adults with depression and mild cognitive impairment. J Affect Disord 239:30–36. https://doi.org/10.1016/j.jad.2018.06.029