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Positron emission tomography neuroimaging in neurodegenerative diseases: Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis

Krzysztof Barc[1], Magdalena Kuźma-Kozakiewicz[1, 2, 3]

[1]Department of Neurology, University Clinical Centre of Medical University of Warsaw, Warsaw, Poland
[2]Department of Neurology, Medical University of Warsaw, Warsaw, Poland
[3]Neurodegenerative Disease Research Group, Medical University of Warsaw, Warsaw, Poland

ABSTRACT

Neurodegenerative diseases are a growing problem of ageing societies. Their insidious onset, and the lack of reliable biomarkers, result in significant diagnosis delays. This article summarises the results of studies on the use of positron emission tomography (PET) in the diagnosis of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. It focuses on clinical-pathogenetic aspects of individual diseases, as well as disease-specific patterns relevant in differential diagnosis and in assessing the risk of disease development and prognosis.

Key words: Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, positron emission tomography

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Introduction

Positron emission tomography (PET) is a nuclear functional imaging technique that enables an assessment of physiological parameters, such as metabolic rate, receptor density or protein deposition. The images are obtained with scanners detecting radioactive ligands usually administered intravenously (Tab. 1). Radiotracers used in PET imaging are mainly labelled with carbon-11 or fluorine-18. Carbon-11 labelled radiotracers have a short half-life time of 20 minutes, which requires a cyclotron on-site and restricts their use only to highly specialised hospitals. With a half-life time of 110 minutes, fluorine-18 labelled radiotracers can be manufactured off-site and transferred to the place of administration [1]. Although considerable information can be acquired from the PET functional image (especially if the functional signal is preserved), a detailed anatomical analysis may require normalisation by image fusion of PET and computed tomography (CT) or magnetic resonance imaging (MRI) [2].

Alzheimer's disease

Alzheimer's disease (AD) is a chronic neurodegenerative disease with an accumulation of amyloid-β (Aβ) and hyperphosphorylated tau proteins resulting in the formation of amyloid plaques (AP) and neurofibrillary tangles (NFTs). It is characterised by a progressive decline in memory functions, deterioration of other cognitive abilities (language functions, visuospatial abilities, complex tasks involving planning/handling), as well as changes in behaviour and personality. In 2015 dementia was estimated to affect 46.8 million people worldwide, with AD being its most common cause. This number is expected to double every 20 years [3].

PET in diagnosis of AD

The majority of PET studies in AD are performed with two groups of radioligands: biomarkers of neuronal dysfunction, and biomarkers of Aβ and tau protein depositions.

Address for correspondence: Magdalena Kuźma-Kozakiewicz, Department of Neurology, University Clinical Centre of Medical University of Warsaw, Warsaw, Poland, e-mail: mkuzma@wum.edu.pl

Table 1. PET radioligands used in diagnostics of neurodegenerative diseases

PET radioligand (short names)	Target	Clinical utility
^{18}F-FDDNP	amyloid-β (Aβ) and tau-protein *assessing* Aβ and tau-protein depositions	diagnosis and evaluation of AD (*^{18}F-FDDNP*); differentiating between PSP and PD (*^{18}F-FDDNP*)
^{18}F-AV-1451 (T807), *^{18}F-T808,* *^{18}F-THK-5105,* *^{18}F-THK-5117,* *^{18}F-THK-5351,* *^{11}C-PBB3*	tau-protein *assessing tau-protein depositions*	diagnosis of AD (*^{18}F-THK-5351, ^{11}C-PBB3*); evaluation of AD (*^{18}F-AV-1451, ^{11}C-PBB3*); differentiating between AD and CN/MCI (*^{18}F-THK-5351, ^{11}C-PBB3*)
^{11}C-PiB, *florbetapir,* *florbetaben,* *flutemetamol,* *^{3}H-BF-227,* *^{18}F-AZD4694 (^{18}F-NAV4694)*	amyloid-β (Aβ) *assessing* Aβ depositions	diagnosis of AD (*^{11}C-PiB, florbetapir, florbetaben, flutemetamol*); differentiating between AD and CN/MCI or FTD (*^{11}C-PiB, florbetapir*); predicting the MCI-AD conversion (*^{11}C-PiB*)
^{11}C-MP4A	acetylcholinesterase enzyme *assessing the brain acetylcholinesterase activity*	diagnosis of AD (*^{11}C-MP4A*); differentiating between AD and DLB (*^{11}C-MP4A*)
^{18}F-DOPA, *^{18}F-FMT*	amino acid decarboxylase *assessing striatal dopaminergic presynaptic function*	diagnosis and evaluation of PD (*^{18}F-DOPA, ^{18}F-FMT*); differentiating between PD and APS (*^{18}F-DOPA*)
^{11}C-CFT, *^{18}F-beta-CFT,* *^{11}C-MP,* *^{11}C-FE-CIT,* *^{11}C-PE2I,* *^{18}F-FP-CIT*	dopamine transporter (DAT) *assessing DAT distribution*	diagnosis of PD (*^{11}C-CFT, ^{18}F-beta-CFT, ^{11}C-MP, ^{11}C-FE-CIT, ^{11}C-PE2I, ^{18}F-FP-CIT);* evaluation and prognosis of PD (*^{18}F-beta-CFT, ^{18}F-FP-CIT*); differentiating between PD and APS (*^{11}C-PE2I, ^{18}F-FP-CIT*); differentiating between PD and ET (*^{11}C-FE-CIT*); differentiating between MSA-P and MSA-C (*^{11}C-CFT*)
^{11}C-DTBZ, *^{18}F-AV-133 (florbenazine)*	vesicular monoamine transporter 2 (VMAT2) *assessing VMAT2 distribution*	diagnosis of PD (*^{11}C-DTBZ, ^{18}F-AV-133*); differentiating between DLB and AD (*^{18}F-AV-133*); evaluation of cognitive performance in DLB (*^{18}F-AV-133*); evaluation of motor performance in PD (*^{11}C-DTBZ*)
^{11}C-raclopride, *^{11}C-n-methylspiperone,* *^{11}C-FLB 457,* *^{18}F-fallypride,* *^{18}F-desmethoxyfallypride*	D2 receptor *assessing postsynaptic dopaminergic function*	diagnosis of PD (*^{11}C-raclopride, ^{18}F-fallypride*); differentiating between PD and APS (*^{18}F-desmethoxyfallypride*); assessing the risk of developing "wearing-off" fluctuations (*^{11}C-raclopride*)
^{11}C-(R)-PK11195, *^{11}C-PBR28*	translocator protein-18 kDa (TSPO) *assessing microglia activation*	differentiating between PDD and non-demented PD (*^{11}C-(R)-PK11195);* diagnosis of ALS (*^{11}C-(R)-PK11195*)
^{11}C-flumazenil	GABA-A *assessing GABA-ergic function*	diagnosis, evaluation and prognosis of ALS (*^{11}C-flumazenil*); differentiating between ALS and PLS (*^{11}C-flumazenil*)
^{11}C-deprenyl-D2	MAO-B *assessing astrocytosis activation*	diagnosis of ALS (*^{11}C-deprenyl-D2*)

PET — positron emission tomography; AD — Alzheimer's disease; PSP — progressive supranuclear palsy; PD — Parkinson's disease; CN — cognitively normal; MCI — mild cognitive impairment; FTD — frontotemporal dementia; DLB — dementia with Lewy bodies; ET —essential tremor; MSA-P — multiple systemic atrophy-parkinsonian; MSA-C — multiple systemic atrophy-cerebellar; PDD — Parkinson's disease dementia; APS — atypical parkinsonian syndromes; ALS — amyotrophic lateral sclerosis; PLS — primary lateral sclerosis

^{18}F-FDG

Neuronal dysfunction is mainly evaluated with ^{18}F-fluorodeoxy-glucose (^{18}F-FDG), a well-established biomarker of cerebral glucose metabolism. Glucose uptake in AD patients is characterised by hypometabolism in posterior cingulate-precuneas, posterior lateral and medial temporal-parietal association cortex and lateral frontal cortex [4–7] (Tab. 2). A more pronounced and extensive hypometabolism is present in early-onset compared to late-onset AD [8]. Interestingly, reaching the same severity of clinical dementia requires a greater hypometabolism in early- as compared to late-onset disease [8]. Both the aphasic (aphasic AD) and the posterior cortical atrophy (PCA) variant of AD (visuospatial AD), present different glucose uptake patterns when compared to typical AD (memory AD). A marked lateralisation of the hypometabolism to the left hemisphere has been found in the aphasic form of AD, while predominant posterior temporoparietal and occipital hypometabolism has been found in the visuospatial

Table 2. Glucose uptake patterns in neurodegenerative disorders

Disorder	Prevalent pattern		Anatomical distribution of glucose uptake patterns										
	Hypermetabolism	Hypometabolism	Cerebrum cortex				Basal Ganglia	Thalamus	Cerebellum	Brainstem	Anterior cingulate	Posterior cingulate	References
			Frontal	Parietal	Temporal	Occipital							
Alzheimer's Disease	-	predominantly in posterior regions: posterior temporoparietal association cortex and posterior cingulate cortex	↓	↓ (spared SMC)	↓ (posterior part)	Normal/↓	N	N	N	N	N	↓	68–73
Frontotemporal Dementia	-	predominantly in anterior regions: frontal lobes, anterior temporal cortex and anterior cingulate cortex	↓	N	↓ (TP)	N	N/↓^{a}	N/↓^{a}	N	N	↓	N	6, 53, 54
Dementia with Lewy bodies	-	occipitoparietal area with the preservation of the posterior cingulate region (cingulate island sign)	↓	↓	↓	↓ (PVC)	N/↓	↓	N	N	N	↓	9, 59, 60
Idiopathic Parkinson's Disease	dorsolateral putamen, globus pallidus, thalami, pontine, cerebellar, cortical motor area	dorsolateral prefrontal cortices and parietooccipital cortices	↓	↓	↓	↓	↑	↑	↑	↑	↓	N	88–91
Multiple System Atrophy	bilateral frontal and superior parietal cortices, bilateral thalamus	bilateral dorsolateral putamen, cerebellum and pons	↑	↑	↑/↓	↓	↓	↑	↓	↓	↓	N	60, 88, 89, 108, 109
Progressive Supranuclear Palsy	bilateral: cortical motor areas, parietal cortex, thalamus and caudate nuclei	brainstem (especially midbrain), midline frontals regions -	↑	↑	↓	N	↑	↑	N	↓	↓ (predominantly)	↓	60, 88, 89
Corticobasal Degeneration	-	asymmetrical, contralaterally to the most affected side: parietal cortices and basal ganglia	↓	↓	↓	N	↓	↓	N	↓	↓	N	88, 89, 104, 115, 116
Amyotrophic Lateral Sclerosis	midbrain, temporal pole, hippocampus and cerebellum	frontal, motor and occipital cortex	↓	↓	↑ (TP)	↓	↓ (↑ LGP)	N	↑	↑ (predominantly midbrain)	↓	N	136–138

LGP — Lateral Globus Pallidus; TP — temporal pole; SMC — sensory motor cortex; PVC — primary visual cortex; ↓ — decreased metabolism; ↑ — increased metabolism; N — normal; ^{a} in advanced stage

variant [9]. Additionally, the retention of a tau radioligand, ^{18}F-AV-1451, significantly differs between typical and atypical AD and also between visuospatial and aphasic (logopenic) AD [10, 11]. In a meta-analysis of ^{18}F-FDG PET studies with cognitively normal controls, the pooled sensitivity and specificity in distinguishing AD from healthy controls (HCs) were 86% and 86%, respectively [12]. ^{18}F-FDG PET imaging has a superior diagnostic accuracy in distinguishing AD from non-demented patients or individuals with mild cognitive impairment (MCI) compared to other diagnostic methods such as clinical guideline, CSF biomarkers, MRI, CT and SPECT [13]. AD-related hypometabolism pattern correlates significantly with disease severity assessed with Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale–Cognitive scales and Everyday Cognition scale [14, 15].

Aβ and tau tracers

Although Aβ and tau protein brain depositions are the neuropathological hallmarks of AD, neither of them is AD-specific. Positive Aβ scans are also present in dementia with Lewy bodies (DLB), cerebral amyloid angiopathy (CAA), and in up to 35% of cognitively unimpaired individuals > 60 years [16–18]. Positive tau protein scans are also seen in tau positive frontotemporal lobar degeneration (FTLD-tau), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and chronic traumatic encephalopathy. Interestingly, FTLD with TDP43 (FTLD-TDP), which is a non-tau pathology disorder, presents positive tau protein scans. This suggests an off-target binding of the radiotracers [19–24]. On the other hand, negative AP PET scans are obtained in rare forms of AD with unusual amyloid plaques that cannot be detected with commonly used Aβ tracers.

Developed in 1999, 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl) amino]-2-naphthyl}ethylidene) malononitrile (^{18}F-FDDNP) was the first PET radiotracer to be used effectively in the visualisation of AD pathophysiology in living humans [25, 26]. It non-selectively binds to both AP and NFTs, but is less sensitive for tau deposits detection compared to further-mentioned radiotracers. Global brain ^{18}F-FDDNP uptake is significantly higher in AD patients compared to HCs. Its binding in the anterior cingulate and frontal region correlates inversely with MMSE score, while the neocortex uptake strongly correlates with cell losses in the hippocampus [27, 28]. A significantly lower global retention of ^{18}F-FDDNP has been shown in HCs compared to MCI and in MCI compared to AD [29].

Tau tracers

Post mortem histopathological studies have shown a stronger correlation of neuronal loss and MMSE score with NFTs compared to AP deposits [30, 31]. The group of tau protein radiotracers include ^{18}F-AV-1451 (T807), T808, ^{18}F-THK-5105, ^{18}F-THK-5117, ^{18}F-THK-5351 and ^{11}C-PBB3. High T807 binding is present in both MCI and AD patients, and is especially marked in the inferior temporal gyrus where its uptake correlates with MMSE and Clinical Dementia Rating scale sum of boxes (CDR-SOB) [32, 33]. Its use is however limited due to a significant off-target binding, including iron, neuromelanin, and MAO [34–36]. ^{18}F-THK-5351 retention differs significantly in AD compared to HCs or MCI and it correlates with neuropsychological tests in both MCI and AD patients. It also inversely correlates with the FDG uptake [37, 38]. ^{11}C-PBB3A neocortex retention is significantly higher in AD compared to HCs and its uptake in the frontal and temporo-parietal junctions correlates inversely with MMSE [39]. The short half-life time of this radiotracer restricts its clinical use, and a fluorine-18 labelled PBB3 is expected to be developed in the near future.

Aβ tracers

A retention of Aβ PET tracers highly correlates with brain biopsy findings [40, 41]. The first Aβ plaques PET radioligand was the Carbon-11-labelled Pittsburgh compound B (^{11}C-PiB) with a pilot human study performed in 2002 and the first peer-reviewed article published in 2004 [42, 43]. The ^{11}C-PiB retention in AD is most prominent in the frontal cortex, followed by the parietal, temporal and occipital cortex and the striatum, compared to HCs [43]. ^{11}C-PiB retention negatively correlates with glucose uptake but not with MMSE or CDR [43, 44]. Other Aβ amyloid tracers include fluorine-18-labelled radioligands such as florbetapir, florbetaben and flutemetamol, all approved for clinical use by the US Food and Drug Administration (FDA). An analysis of seven AD individuals showed a thorough agreement between visual reads of flutemetamol PET scans and histological brain biopsy findings [45]. In a meta-analysis of 19 studies, the pooled sensitivity and specificity rates in distinguishing AD from HCs for florbetapir were 89.6% and 87.2%, and for florbetaben 89.3% and 87.6%, respectively, while in a phase II trial with flutemetamol they were 93.1% and 93.3% [46, 47]. A prospective study of 211 patients suspected of early-onset dementia showed that the addition of flutemetamol PET imaging to clinical examination, medical history, laboratory tests, brain MRI and neuropsychological testing, increased the diagnostic confidence from 69% ± 12% to 88% ± 15%. The study resulted in a change of diagnosis in 19% and initiation of treatments in 37% of patients with AD [48]. In the early stage of the disease, amyloid PET imaging showed as high an accuracy in AD diagnosis as Aβ42/total tau or Aβ42/hyperphosphorylated tau CSF. A combination of CSF and PET biomarkers were not however able to increase the diagnostic accuracy [49]. In recent years both flutemetamol and florbetapir have become widely available in the US and Western Europe and have been used in a number of clinical trials. Other accessible Aβ selective biomarkers clearly differentiating AD from HCs are BF-227 and ^{18}F-AZD4694 (NAV4694) [50, 51].

PET in differential diagnosis of AD

Determining the cause of dementia is challenging, even for specialists. Accurate diagnosis is essential because each dementia subtype has a specific mechanism, treatment, family risk, and prognosis.

AD vs FTD

Frontotemporal dementia (FTD) is a neurodegenerative disease characterised by progressive deficits in behaviour, executive functions, or language. Its pathological hallmark is the degeneration of the prefrontal and anterior temporal cortices [52]. Cognitive impairment may be absent in the prodromal phase with only behavioural changes, which can lead to an erroneous diagnosis of psychiatric disorder. The behavioural variant of FTD can also clinically overlap with the frontal variant of AD as both disorders develop behavioural changes. ^{18}F-FDG PET imaging in FTD patients shows hypometabolism predominantly in anterior regions: frontal lobes, anterior temporal cortex and anterior cingulate cortex, while in AD the hypometabolism is present in posterior regions including posterior temporoparietal association cortex and posterior cingulate cortex [6, 53, 54] (Tab. 2). The sensitivity and specificity rates for differentiating AD from FTD with ^{18}F-FDG PET imaging have been estimated at 99% and 65%, respectively [55]. Interestingly, ^{18}F-FDG PET imaging is superior to clinical assessment in differentiating AD and FTD by an experienced dementia specialist, reaching a diagnostic accuracy of 89.6% [56]. As Aβ protein depositions are not features of FTD, there is a significantly lower florbetapir uptake compared to AD [57]. A study performed in 62 AD and 45 FTLD patients showed a higher sensitivity rate for ^{11}C-PiB-PET visual read (89% *vs* 73%) and higher specificity for ^{18}FDG PET visual read (83% *vs* 98%) in differentiating AD from FTD [58].

AD vs DLB

DLB accounts for 20% of late-onset dementias. Its pathological hallmark is the presence of Lewy bodies within the neocortical and limbic regions and usually deposits of AP and NFTs. It is characterised by cognitive fluctuations, visual hallucinations and spontaneous features of parkinsonism. DLB may present a clinical overlap with AD in terms of cognitive impairment with executive and memory dysfunction and spontaneous parkinsonism. The glucose uptake pattern in DLB is characterised by a predominant occipito-parietal hypometabolism with the preservation of the posterior cingulate region presenting a 'cingulate island sign' on PET scans (Tab. 2) [9, 59, 60]. Revised criteria for the clinical diagnosis of probable and possible DLB have included ^{18}F-FDG PET imaging as a supportive biomarker. The sensitivity and specificity rates for differentiating DLB from FTD with ^{18}F-FDG imaging have been estimated to be 71% and 65%, respectively [55]. Since the deposition of Aβ is present in the majority of DLB patients, Aβ tracers are not useful in differentiating DLB from AD. However, high neocortical Aβ cortical deposits are associated with a shorter prodromal phase in DLB [16]. ^{18}F-AV-133, a biomarker of dopaminergic nigrostratial function, has a > 95% accuracy in differentiating DLB from AD and significantly correlates with cognitive performance in DLB patients [61, 62]. The combination of dopaminergic tracers and FDG has been shown to be useful in differentiating DLB from AD, Parkinson's disease (PD) and HCs [63]. Also, brain acetylcholinesterase (AChE) activity, measured with N-[11C]-methyl-4-piperidyl acetate (^{11}C-MP4A), reveals a significant difference between AD and DLB [64].

AD vs VD

Although vascular dementia (VD) is the biggest clinical challenge in differential diagnosis of AD, it is primarily evaluated by MRI [65]. ^{18}F-FDG PET scans reveal cortical and subcortical hypometabolism areas corresponding to signal changes in MRI.

In the most recent European Association of Nuclear Medicine (EANM) and European Academy of Neurology (EAN) recommendations for the use of brain FDG PET in neurodegenerative cognitive impairment and dementia, the panel agreed on recommending ^{18}F-FDG PET in diagnosing MCI due to AD, FTLD or DLB, in the diagnosis of atypical AD and pseudodementia, and in differentiating between AD and DLB, FTLD or VD, and between DLB and FTLD [66].

PET in prognosis of AD

Patients with MCI are at a higher risk for developing AD, with an estimated conversion rate of 10% to 15% per year [67]. In a one-year follow-up study performed in 37 MCI patients, all eight individuals who converted to AD showed reduced cerebral glucose metabolic rates in the inferior parietal cortex, in contrast to the non-converters [68]. Moreover, among APOE4 genotype positive groups, a prediction of conversion to AD reached the sensitivity of 100% and the specificity of 90%. Bilateral hypometabolism in the medial temporal cortex is also linked to a higher risk of conversion, while hypometabolism in the dorsolateral frontal cortex is present in stable MCI patients [69, 70]. The presence of the APOE4 gene in cognitively unimpaired individuals is linked with significant hypometabolism in posterior cingulate, parietal, temporal and prefrontal cortex as observed in the group with probable AD [71, 72]. A large meta-analysis that included six ^{18}F-FDG-PET studies with 280 patients showed a ^{18}F-FDG PET imaging sensitivity of 88.9% and specificity of 84.9% in the prediction of conversion to AD in patients with MCI. The results were more accurate than SPECT and structural MRI [73]. Positive ^{11}C-PiB scans in MCI patients at baseline strongly predicted conversion to AD, although negative ^{11}C-PiB scans did not exclude a further conversion [74–76]. ^{11}C-PiB PET imaging was able to clearly distinguish MCI from AD and MCI from HCs, and to differentiate those groups better than ^{18}F-FDG PET imaging [77–79].

A combination of markers including hippocampal volumetry (Hippo), ^{18}F-FDG PET, amyloid PET and CSF Aβ42 has a good predictive value in assessing the risk of conversion of MCI patients to AD. In a seven-year follow-up study, 73 patients were divided into four groups depending on biomarker positivity. The lowest conversion rate (5%) was reported for Aβ42(-),^{18}F-FDG-PET(-) Hippo(-), while the highest (100%) for concomitant Aβ42(+), ^{18}F-FDG-PET(+) and Hippo(+). The latter was also found to convert in the shortest time [80].

PET in progression and treatment of AD

^{18}F-FDG-PET has been established as a sensitive marker of disease progression of AD in a one-year follow-up study. On the other hand, ^{11}C-PiB-PET retention remained stable in a two-year observation [4, 81]. A significant decline in AD-related glucose uptake pattern was observed in a one-year follow-up study in a non-treated group compared to a rivastigmine-treated group [82]. A similar outcome was obtained in a 24-week follow-up study with donepezil [83].

Parkinson's disease

PD is the second most common neurodegenerative disorder after AD. It is characterised by a dopaminergic neuronal loss in substantia nigra caused by intraneuronal proteinaceous inclusions, called Lewy bodies, mainly composed of α-synuclein. The diagnosis of PD is based on clinical criteria including bradykinesia, rigidity, resting tremor and postural instability. With disease progression, non-motor features such as cognitive decline, depression, psychosis, sleep dysfunction and dysautonomia may also be present [84, 85].

PET in diagnosis of PD

The most commonly used radioligands in PD PET studies are ^{18}F-FDG and dopamine-specific radiotracers that can be divided into three groups: biomarkers of dopamine (DA) synthesis (^{18}F-DOPA); biomarkers of synaptic dopamine transporters (DAT) (^{11}C-CFT, ^{11}C-MP, ^{11}C-FECIT, ^{11}C-PE2I, ^{18}F-FP-CIT) and vesicle monoamine transporters (VMAT2) (^{11}C-DTBZ, ^{18}F-AV-133); and biomarkers of postsynaptic dopaminergic function (D2/3 receptors, D2/3) (^{11}C-raclopride, ^{11}C-n-methylspiperone, ^{11}C-FLB 457, ^{18}F-fallypride, ^{18}F-desmethoxyfallypride) (Tab. 1). Other radioligands used in PD PET imaging include microglia activation biomarkers (^{11}C-(R)-PK11195) and AChE activation biomarkers (^{11}C-MP4P) [86, 87].

^{18}F-FDG

A PD-related pattern is characterised by hypermetabolism in the basal ganglia, ventral thalamus, pons and cerebellum with concurrent hypometabolism in the dorsolateral prefrontal, posterior parietal and occipital cortex [88-91] (Tab. 2). Its expression correlates positively with Hoehn and Yahr (H&Y) and Unified Parkinson's disease rating scale (UPDRS) motor scores [90].

Dopamine-specific tracers

Radiotracers assessing dopaminergic function are useful in PD diagnosis. There is a significant reduction of ^{18}F-DOPA uptake in the caudate nucleus and putamen and the ^{11}C-CFT uptake in the posterior putamen compared to HCs [92, 93]. Interestingly, a different ^{11}C-CFT distribution occurs in young-onset PD, where caudate nuclei are more spared compared to putamen. The late-onset subtype is characterised by a more uniform pattern [94]. As dopaminergic tracers' retention inversely correlates with motor disability (UPDRS motor scores in case of $_{18}$F-DOPA, $_{11}$C-CFT, $_{18}$F-FP-CIT and $_{18}$F-DTBZ), these may be useful in the evaluation of disease progression [94–96]. Furthermore, the retention of DAT (^{11}C-CFT) and VMAT2 (^{18}F-DTBZ) correlates with disease duration [94, 96].

Due to up-regulation of D2 receptors, D2/D3 tracer uptake is usually increased in PD [97]. A recent publication considering 18F-fallypride, one of the D2/D3 tracers, presented a significantly reduced retention in PD compared to HCs and a correlation between its uptake in the putamen and globus pallidus with UPDRS [98].

Non-motor dysfunctions in PD

PET has also been used in the assessment of psycho-behavioural and olfactory dysfunction. Limbic AChE activity correlates positively with cognitive and memory functions, but not with visuospatial functions [87]. While PD-dementia (PDD) is associated with a generalised cortical hypometabolism, PD-MCI patients develop hypometabolism in the temporoparietooccipital junction and the frontal cortex [99–101]. ^{11}C-(R)-PK11195-uptake, reflecting microglia activation, is significantly increased in cingulate, striatum and neocortex in PDD compared to HCs, and in the left parietal lobe in PDD compared to non-demented PD patients, and correlates inversely with MMSE score [86].

Hyposmic PD shows significantly reduced DAT (^{18}F-FP-CIT) binding in bilateral caudates and in left anterior and posterior putamen compared to normosmic PD patients [96]. Also the degree of DAT uptake (^{18}F-FP-CIT, ^{11}C-β-CFT) in the hippocampus, amygdala and striatum, VMAT2 (^{11}C-dihydrotetrabenazine) in the striatum and AChE activity tracer (^{11}C-MP4P) in the hippocampus, amygdala and neocortex correlates with the University of Pennsylvania Smell Identification Test (UPSIT) scores [87, 102, 103].

PET in differential diagnosis of PD

Due to its different prognosis and response to pharmacological and surgical treatment, it is especially important to differentiate PD from other diseases with parkinsonian features (known as atypical parkinsonian syndromes, APS), such as multiple system atrophy (MSA) and PSP, accounting together for 80% of misdiagnosed PD, as well as CBD and DLB [104].

Putamen hypermetabolism is one of the crucial elements of PDRP and the only feature distinguishing PD from APS [88, 89]. However, along with disease progression, the metabolism of the putamen normalises turning hypometabolic in the advanced stage, which may decrease its usefulness in differentiating a diagnosis [88, 89, 105]. An analysis of putamen-related parameters including posterior putamen binding, posterior-to-anterior putamen ratio, and posterior putamen-to-caudate with D2/3 receptor ligand (18F-DMFP) results in high sensitivity, specificity and accuracy (92%, 96% and 94%, respectively) in distinguishing PD from APS [106, 107].

PD vs MSA

MSA is characterised by a combination of parkinsonism, autonomic dysfunction, and cerebellar ataxia. Bilateral cerebellar and putaminal hypometabolism are distinguishing PET features of the disease [60, 88, 89]. Cerebellar hypometabolism is present in both patients with cerebellar dysfunction (MSA-C) and those without ataxia (MSA-P) [89]. Although not all MSA-P patients present cerebellar hypometabolism, it is rarely observed in other parkinsonian condition. Only a few MSA patients develop parietal hypometabolism, while it is a common finding in non-demented PD patients [108]. A significant correlation has been found between the degree of cerebellum and pons hypometabolism and cerebral ataxia and autonomic dysfunction. No such correlation has been observed between striatal hypometabolism and the severity of parkinsonism [109]. ^{18}F-FDG-PET sensitivity/specificity rates in the clinical diagnosis of MSA are 76%/98% with visual reading, and 96%/99% with statistical parametric mapping (SPM)-supported reading, respectively [89]. MSA-P patients present more pronounced DAT (^{11}C-CFT) reduction compared to MSA-C [110].

PD vs PSP

PSP is clinically characterised by a vertical gaze dysfunction, extrapyramidal features and cognitive decline. The specific glucose uptake pattern in PSP is characterised by bilateral reduction of metabolism in midline frontal regions and in the brainstem [60, 88, 89]. The evaluated sensitivity and specificity rates in the clinical diagnosis of PSP with the ^{18}F-FDG-PET visual reading are 60% and 96%, respectively, and with SPM-supported reading they account for 85% and 99% [89]. Caudate ^{18}F-dopa uptake is significantly lower in PSP compared to PD, and equally decreased in anterior and posterior putamen in PSP, in contrast to PD where the anterior putamen is relatively spared [92]. Since PSP is a tauopathy, tau radiotracers are useful in differentiating PSP from PD. ^{18}F-FDDNP shows a distinctive pattern at early disease stages and its binding in the frontal lobe correlates with the PSP rating scale (PSPRS) score [111]. High ^{18}F-AV-1451 uptake within the putamen, pallidum, thalamus, midbrain and dentate nucleus of the cerebellum is observed in PSP compared to HCs, and it also correlates with the PSP clinical severity score [112–114]. Compared to healthy individuals, PSP is also characterised by a higher ^{11}C-PBB uptake in globus pallidus, putamen, thalamus, subthalamus, midbrain, pons and peri-rolandic areas [23].

PD vs CBD

CBD is a neurodegenerative disease classified as a primary tauopathy characterised by progressive asymmetric rigidity and apraxia accompanied by other cortical and extrapyramidal dysfunction features [115]. The specific glucose uptake pattern in CBD is characterised by asymmetric basal ganglia and cerebral cortical hypometabolism, mainly expressed in frontoparietal area, contralateral to the clinically more affected side, and a bilateral occipital region hypermetabolism [88, 89, 116]. The sensitivity and specificity rates in the clinical diagnosis of CBD with ^{18}F-FDG-PET visual reading are 91% and 92%, respectively, and with SPM-supported reading they account for 91% and 99% [89]. The patterns of glucose and levodopa uptake differ in the early stages of CBD and PD [118]. Compared to HCs, CBD is characterised by a high retention of ^{11}C-PBB3 in the peri-rolandic areas, supplementary motor area, subthalamus and midbrain, with greater binding in basal ganglia contralaterally to the affected side [23]. Both ^{18}F-AV-1451 and ^{18}F-THK-5351 retention patterns are able to clearly differentiate CBD from HCs and AD, while ^{18}F-AV-1451 - from PSP [118, 119].

Interestingly, ^{18}F-FDG PET imaging has been found to be as predictive in risk stratification of APS as a one-year clinical follow-up. It was also superior to SPECT in differential diagnosis of APS [120, 121].

PET in assessment of treatment efficacy in PD

Long-term PD treatment results in late motor complications, such as fluctuations and dyskinesia. Patients who are at risk of developing 'wearing-off' fluctuations present significantly less expressed dopamine transporter activity in the putamen at baseline. Compared to individuals not experiencing 'wearing-off', they have been found to have a three times higher synaptic level of dopamine (measured with ^{11}C-raclopride) at one hour and no changes at four hours after oral administration of levodopa [122–124]. Marked DAT impairment in the posterior putamen at baseline is significantly associated with early appearance of levodopa-induced bradykinesia [125]. The long-time effect of PD pharmacological treatment assessed with PET studies showed a slower loss of striatal dopamine storage in patients treated with ropinirole compared to levodopa [126]. PD-related pattern (PDRP) decreases after subthalamotomy, deep brain stimulation (DBS) of the subthalamic nucleus (STN) and levodopa treatment, showing a correlation with clinical improvement after therapy [127, 128]. PET studies have been introduced into clinical trials including gene or cell therapy, but their outcomes do not always correlate with clinical improvement [129].

PET in prognosis of PD

Dysfunction of nucleus accumbens and orbitofrontal cortex on the clinically intact side, presented with reduced dopamine transporter radiotracer (^{11}C-CFT) uptake, positively correlates with the interval of developing bilateral parkinsonism [130]. Idiopathic rapid eye movement sleep behaviour disorder (iRBD) is considered to be one of the predictors of developing PD. In a clinical follow-up study of 10 iRBD patients and 10 HCs the phenoconversion to PD/DLB was more likely in individuals with high PDRP at baseline. In contrast, the iRBD patients who developed MSA 2–4 years later had not expressed the PDRP at baseline [131, 132]. De novo PD patients with RBD present more pronounced hypometabolism in posterior cortical regions and anterior cortical regions of the more affected side, as well as a dopaminergic impairment of caudate nuclei and putamen measured with DAT uptake compared to non-RBD PD patients [133, 134]. Interestingly, iRPD patients present a significantly higher putamen/caudate ratio than both RBD-PD and non-RBD PD [134].

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting the upper and lower motor neuron resulting in progressive neuromuscular weakness. The pathogenesis of the disease still remains unclear. Approximately 50% of patients develop language and executive dysfunction in the course of the disease, while 15% develop FTD (FTD-ALS) [135].

PET in diagnosis of ALS

^{18}F-FDG

The majority of ALS PET studies have been performed with ^{18}F-FDG. ALS glucose-uptake pattern is characterised by hypometabolism in frontal, motor, and occipital cortex and hypermetabolism in cerebellum, midbrain, temporal pole and hippocampus [136–138]. In a study with 195 ALS patients, significantly more expressed hypometabolism in left motor and premotor cortex was present in bulbar as compared to spinal onset patients [137]. In another study with 13 bulbar and 19 spinal onset patients, similar patterns were observed, but with no significant difference between the two groups. In ALS patients with spinal onset, there was a relative hypermetabolism in the right midbrain compared to HCs [136]. No meta-analysis of the sensitivity and specificity in discriminating ALS patients from controls has been performed to date. A one-year follow-up study performed in 195 ALS patients and 40 controls showed a sensitivity of 95.4% and specificity of 82.5% in discriminating both groups with ^{18}F-FDG imaging at baseline [137].

Other tracers

A significantly lower uptake of a GABA-A biomarker (^{11}C-flumazenil) has been found in the prefrontal, parietal, visual association and left motor and premotor cortex of ALS patients compared to HCs [139]. This may be due to the loss or dysfunction of inhibitory GABA-ergic neurons in ALS patients. Compared to HCs, sporadic ALS (sALS) show decreased cortical ^{11}C-flumazenil uptake predominantly in the premotor regions, motor cortex and posterior motor associated areas. Patients with ALS-linked D90A SOD1 mutation show a decreased radiotracer uptake in the left frontotemporal junction and anterior cingulate of the dominant hemisphere [140]. ^{11}C-flumazenil uptake in sALS correlates with upper motor neuron (UMN) damage, but not with revised ALS functional rating scale (ALSFRS-R), while in ALS SOD1 D90A homozygotes it correlates with ALSFRS-R and disease duration, but not with UMN damage. Patients harbouring a C9orf72 dynamic mutation, the most frequent genetic cause for ALS, present relatively more expressed hypometabolism in the thalamus and posterior cingulate compared to C9orf72-negative individuals [141]. In a study performed in 70 ALS patients (11 C9orf72-positive, 59 C9orf72-negative, 20 HCs), the sensitivity, specificity, and accuracy rates in distinguishing each patient group from HCs were 89.8%, 85.0%, and 88.6% in C9orf72-negative ALS, and 90.9%, 100%, and 96.8%, in C9orf72-positive cases, respectively [141]. Microglia activation, typically increased in ALS motor system, can be assessed with ^{11}C-(R)-PK11195 and ^{11}C-PBR28 radioligands. In a group of 10 ALS patients and 14 HCs, a significantly higher ^{11}C-(R)-PK11195 binding was found in motor cortex, pons, dorsolateral prefrontal cortex and thalamus in ALS patients compared to HCs. There was a correlation between radiotracer uptake in the motor cortex and UMN damage [142]. A significantly increased ^{11}C-PBR28 binding was also observed in the precentral gyrus of ALS patients compared to HCs [143]. ^{11}C-PBR negatively correlated with ALSFRS-R scale and positively with UMN damage, but there was no correlation with disease duration [143]. Bulbar onset patients showed increased ^{11}C-PBR uptake in the brainstem while limb onset in the precentral gyri [143]. Neuronal loss in the central nervous system in ALS patients is accompanied by actrocytosis. As MAO-B is primarily located in astrocytes, actrocytosis activation can be measured with MAO-B radiotracers such as ^{11}C-deprenyl-D2 (^{11}C-DED). A significantly increased binding of ^{11}C-DED has been observed in the pons and white matter of ALS patients compared to HCs [144].

PET in differential diagnosis of ALS

ALS vs FTD-ALS

FTD-ALS patients present more expressed hypometabolism including bilateral premotor, frontal, anterior prefrontal cortex with left predominance, lateral prefrontal and orbitofrontal cortex compared to ALS cognitively normal individuals. Significantly different patterns are also observed between cognitively normal and impaired ALS patients not fulfilling FTD criteria and cognitively impaired non-FTD ALS and ALS-FTD [145]. FTD-ALS patients present hypometabolism in the frontal area, while FTD alone have hypometabolism both in the frontal and temporal areas with a more symmetric pattern presented in FTD-ALS patients [146].

ALS vs PLS vs PMA

There is a significantly more expressed hypometabolism in the prefrontal cortex and posterior cingulate of ALS compared to primary lateral sclerosis (PLS) patients. It is also significantly less expressed in the primary sensorimotor cortex of PLS compared to ALS. The sensitivity and specificity rates allowing a distinction between PLS and HCs are 57.1% and 100%, respectively [141]. ^{11}C-flumazenil binding in anterior frontal and orbito-frontal regions was relative lower in both sALS and D90A SOD1 ALS patients compared to PLS [147]. The glucose-uptake pattern in progressive muscular atrophy (PMA) did not differ from classic ALS, except for a less expressed hypometabolism in the motor cortex and the thalamus [141].

PET in prognosis of ALS

Extensive hypometabolism in the prefrontal or anterior temporal areas is associated with a significantly shorter survival in C9orf72-negative ALS patients [141]. As mentioned before, a reduced ^{11}C-flumazenil uptake in SOD1 D90A homozygotes has been shown to correlate with disease duration [140]. A significantly increased uptake of an oxidative stress biomarker, ^{62}Cu-ATSM, in the bilateral cortices around the central sulcus has been observed in ALS patients compared to HCs. It negatively correlated with ALSFRS-R [148].

Conclusion

PET imaging is a useful diagnostic tool in the assessment of various neurodegenerative diseases (Tab. 2). Specific glucose uptake patterns observed in AD and in other dementias enable physicians to diagnose and differentiate these disorders with high degrees of sensitivity and specificity. A group of accessible Aβ and NFTs radiotracers present high uptake in AD. ^{18}F-FDG-PET imaging can help predict MCI-AD conversion. The glucose uptake patterns characteristic for PD and APS permit the distinction of a number of disorders with parkinsonian features.

This is especially important in cases with different prognoses and responses to treatment. Dopamine radiotracers correlate well with disease severity and can predict further drug-induced motor implications. ^{18}F-FDG and ^{11}C-flumazenil imaging seems to be helpful in the diagnosis of ALS and in differentiating it from PLS as both diseases differ in prognosis.

In recent years, PET imaging has become widely accessible not only in scientific but also in clinical settings. The use of PET in the diagnostic process of neurodegenerative diseases provides the opportunity to decrease diagnosis delay, increase diagnostic confidence, and monitor treatment efficiency.

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