Applications of PET-CT in Neurological Disorders: An Overview

7

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Abbreviations

18F-MPPF	Methoxyphenyl-(*N*-2′-pyridinyl)-*p-fluoro-benzamidoethyipiperazine* that binds to the *serotonin-1A receptor*
AD	Alzheimer disease
AADC	Amino acid decarboxylase
CBS	Corticobasal syndrome
DAT	Dopamine transporter
DLBD	Diffuse Lewy body dementia
DOTATOC	DOTA-Tyr^3-octreotide (a somatostatin analog)
DNA	Deoxyribonucleic acid
FDOPA	*Fl*uorodopa min
F-18 FLT	32-Deoxy-32 fluorothymidine (marker for cellular proliferation)
FTD	Frontotemporal dementia
FMISO	Fluoromisonidazole (a hypoxia imaging agent)
F-18 FDDNP	[F-18]fluoroethyl) (methyl) amino] -2-naphthyl ethylidene malononitrile for studying binding patterns of amyloid plaque and tau tangles in Alzheimer disease
5-HT1A	A subtype of 5-hydroxytryptamine
GLUT	Glucose transporter
C-11 DTBZ	*D*ihydro *t*etra*b*ena*z*ine (used for the study of dopaminergic neuronal function)
C-11 CFT	*C*arbomethoxy-3-â-(4-*f*luorophenyl) *t*ropane (for the study of distribution of *dopamine* transporters in the *brain*)
C-11 MP4A	C-11-labeled N-methyl-4-piperidyl -acetate for measurements of regional acetylcholine esterase activity in degenerative dementia
C-11 PMP	Methylpiperidin-4-yl propionate for the study of brain AChE activity in patients with AD and PD
C-11 CPK	1-[2-Chlorophenyl]-*N*-methyl-*N*-[1-methyl-propyl]-3-isoquinoline carboxamide used for quantification of activated microglia
C-11 PiB	Carbon-11-labeled Pittsburgh compound B, a marker of cortical fibrillar amyloid-beta load
C-11 SCH	A selective dopamine D1 antagonist
5-HT2A	5-Hydroxytryptamine (neurotransmitter serotonin (5-HT))
IPD	Idiopathic Parkinson's disease
MCI	Mild cognitive impairment
MMSE	Mini-mental state examination

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MSA	Multiple system atrophy
PCNSL	Primary CNS lymphoma
PSP	Progressive supranuclear palsy
SPM	Statistical parametric mapping
TLE	Temporal lobe epilepsy
VMAT	Vesicular monoamine transporter
VMAT	Volumetric modulated arc therapy

When positron emission tomography (PET) was introduced into medicine more than 30 years ago, the first organ of major interest was the brain. Presently, the applications of PET in neurology can be divided into the more commonly performed:

1. *Resting brain metabolic studies* using F-18 fluorodeoxyglucose (^{18} F- FDG) PET
2. *Neuroreceptor and brain activation studies* primarily used for research purposes
   The broad areas of neurology where PET studies are being used in clinical practice are as follows:
   - Epilepsy
   - Dementia
   - Movement disorder
   - Stroke
   - Paraneoplastic syndromes
   - Brain tumors
3. *Psychiatric applications*: Psychiatry studies mostly involve the neuroreceptor applications of PET, and are not in routine clinical practice.

The single most commonly utilized PET agent in clinical neurological imaging is ^{18}F-FDG, but the list of promising radioligands used for imaging various aspects of brain function and pathology is increasing. Table 7.1 presents an elaborate list of radioligands that are presently available for neurological PET imaging.

When interpreting ^{18}F-FDG PET (half-life of ^{18}F is 110 min) images, one should keep in mind that the imaged glucose uptake pattern reflects transport and trapping during a prolonged period of time (approximately 35–40 min), thus representing a summation of cellular metabolic processes during the uptake period. Therefore, it is not an ideal agent to

Table 7.1 List of PET radioligands used in neurological imaging

Parameter	PET radioligand	Assessment of cerebral activity
Functional activity		
	F-18 FDG	Glucose metabolism
	O-15 H2O	Blood flow
	C-11 methionine/choline	Amino acid metabolism
	F-18 choline/fluoroethyltyrosine	Amino acid metabolism
Neurotransmitters		
Dopamine	F-18 fluoroDOPA (FDOPA)	Dopamine synthesis
	C-11 raclopride	D2 receptors
	C-11 SCH 23390	D1 receptors
	C-11 DTBZ	VMAT
	C-11 CFT	Dopamine reuptake
Acetylcholine	C-11 PMP	Acetylcholinesterase activity
	C-11 MP4A	Butyrocholinesterase activity
	C-11 methyl-4-piperidinyl-N-butyrate	Nicotinic receptors
	C-11 nicotine	Nicotinic receptors
	F-18 fluoro-A-85380	Muscarinic receptors
	C-11 benztropine	Muscarinic receptors
Serotonin	C-11 WAY-100635	
	18 F-MPPF	5-HT1A receptors
	18 F-altanserin	5-HT2A receptors
Neuro-inflammation	C-11 CPK11195	Glial inflammation
Pathology in vivo	C-11 PiB	Amyloid
	F-18 florbetapir	Amyloid
	F-18 FDDNP	Tau proteins

measure rapid short-term activation neuronal processes, which are better detected by using ^{15}O-labeled water or functional MRI or SPECT perfusion studies.

Epilepsy

Approximately one-third of patients with epilepsy will be medically refractory and will continue having disabling seizures despite an adequate trial of appropriate antiepileptic medications. These patients are assessed for surgical candidacy. This evaluation involves use of clinical, neuropsychological, electrophysiological, and radiological data to determine whether seizure originates from a focal area of the brain—lesional epilepsy. Surgery may be considered the treatment of choice in lesional epilepsy. It has been observed that there is very low probability of long-term seizure freedom without surgery in pharmacoresistant patients. In those patients where the seizure focus is accurately identified and is located in noneloquent brain, complete excision results in good postoperative seizure control.

The principal aim of presurgical evaluation is the lateralization and localization of the epileptogenic zone, which can be achieved in 85 % patients; the remaining 15 % would require intracranial electrodes for this determination. There are no evidence-based guidelines to direct the course of investigations. However, epilepsy teams at surgical centers usually follow set protocols for workup of these patients. Most importantly, there has to be a concordance of interictal scalp EEG, ictal video EEG, and MRI for the epileptogenic focus before patient is taken up for surgery.

Temporal Lobe Epilepsy (TLE)

MRI is the first-line neuroimaging procedure for the localization and lateralization of the epileptogenic lesion, and hippocampal sclerosis, the most common pathological substrate of TLE, can be readily detected by MRI in most cases. ^{18}F-FDG PET is useful in cases with normal or inconclusive MRI (present in 53 %) and in patients with discordant MRI and electroclinical studies. $^{18F\text{-}FDG}$ PET, which was most frequently carried out after unsatisfactory MRI/EEG, influenced surgical decision in 71 % cases, and surgical candidacy was based on ^{18}F-FDG PET findings in 17 % cases. MRI-negative, PET-positive TLE is likely a distinct subgroup of TLE where the pathophysiology more often involves the temporal neocortex rather than being confined to mesial temporal structures. In the case of mesial temporal lobe epilepsy, the minority of patients with electroclinically well-localized temporal lobe seizures but no evidence of hippocampal sclerosis on MRI may be brought to surgery based on hypometabolism seen on ^{18}F-FDG PET in the temporal lobe, assuming it to be the origin of seizures.

Neocortical Epilepsy

^{18}F-FDG PET may detect 70–90 % of cortical dysplasias (Fig. 7.1), the most common pathological substrate of neocortical epilepsies. Interictal PET may be of assistance in nonlesional neocortical epilepsy cases for general localization and for guiding intracranial electrode placement. ^{18}F-FDG PET has been shown to have 71 % overall detection rate in patients with extratemporal epilepsy and normal MRI. Also, many pediatric epilepsy surgery centers routinely perform PET MRI fusion in all cases of epilepsy and have shown an incremental value of PET in localizing dual pathology, cortical dysplasia type I, and mild malformations of cortical development.

Usually, interictal ^{18}F-FDG PET studies are performed because of the duration of tracer uptake (extends over 35–40 min). However, rarely ictal ^{18}F-FDG PET may prove useful in a child with "epilepsia partialis continua" suspected to have "Rasmussen's encephalitis" and a normal MRI. The localization of the epileptogenic focus (which appears hypermetabolic) would justify the use of intravenous immunoglobulin in such patients (see Fig. 7.2).

A number of additional tracers like C-11 flumazenil and C-11 methyl tryptophan have been used for epilepsy imaging, but are presently not available in India.

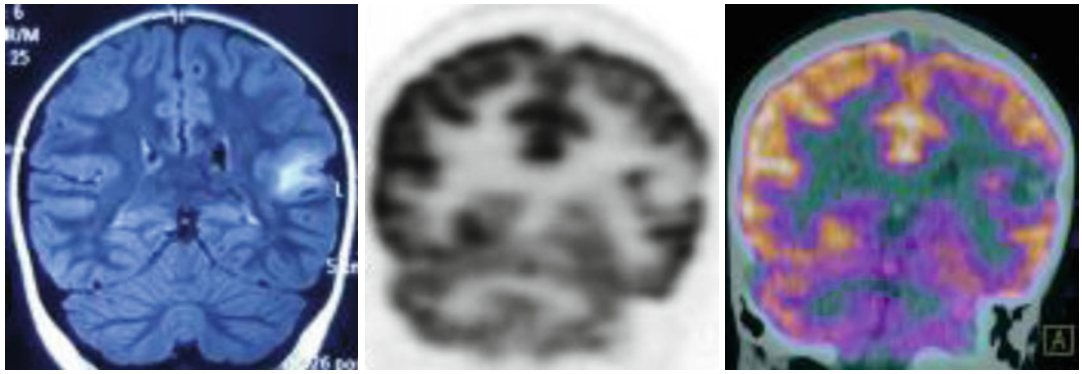

Fig. 7.1 An 11-year-old male child with drug refractory epilepsy. T1W MRI shows cortical dysplasia in the left parietal lobe. Plain ^{18} F-FDG PET and fused PET-CT images show hypometabolism corresponding to the lesion on MRI

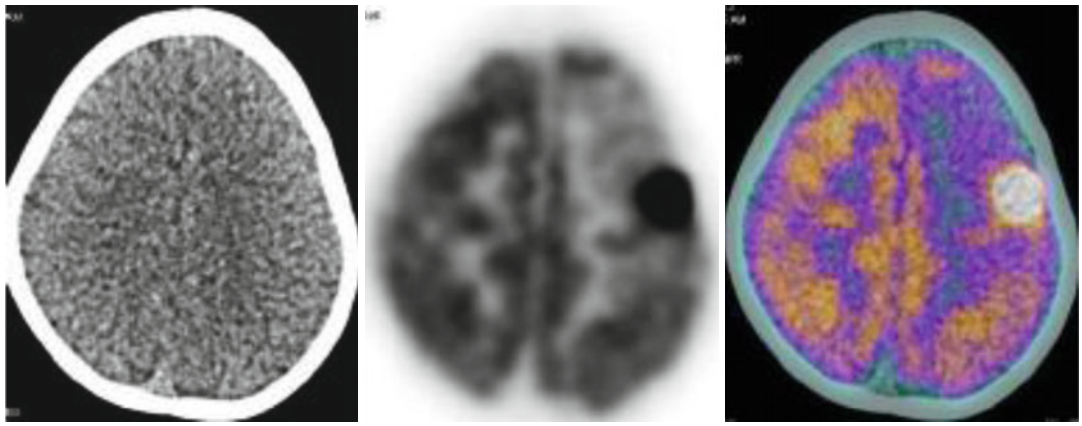

Fig. 7.2 A 3-month-old male child with epilepsia partialis continua and a normal MRI. Pediatric neurologist referred the child for ^{18} F-FDG PET and on the basis of focal hypermetabolism in the left posterior frontal region (which was again reviewed to be normal on MRI) gave the child intravenous immunoglobulin to which he responded

Dementia

Three distinct phases for Alzheimer's dementia (AD) have been described: presymptomatic, mild symptomatic but predementia, and dementia caused by AD. Large collections of data corroborating the power of brain imaging in helping to establish diagnoses and predict cognitive decline are emerging from multicenter international imaging efforts. Also, imaging can effectively be used for differential diagnosis of dementia subtypes.

^{18}F-FDG *PET:* Though the diagnosis of dementia type is primarily clinical, there may be considerable overlap of phenotypes in early cases. Hypometabolism on ^{18}F-FDG PET can be used as a downstream marker of neuronal injury. Specific patterns of hypometabolism on the $^{18F\text{-}FDG}$ PET study have been used for the differential diagnosis of neurodegenerative dementias. Hypometabolism involving the parietotemporal cortices (unilateral or bilateral), including the posterior cingulate and precuneal cortices, is the characteristic metabolic pattern for AD (Fig. 7.3). This is used to differentiate AD from frontotemporal dementia (FTD), which is characterized by hypometabolism in the frontal and temporal cortices (behavioral variant) (Fig. 7.4). ^{18}F-FDG PET has a high sensitivity of 97 and 86 % specificity in distinguishing AD from FTD. Occipital and visual cortices hypometabolism on ^{18}F-FDG PET is useful for differentiating

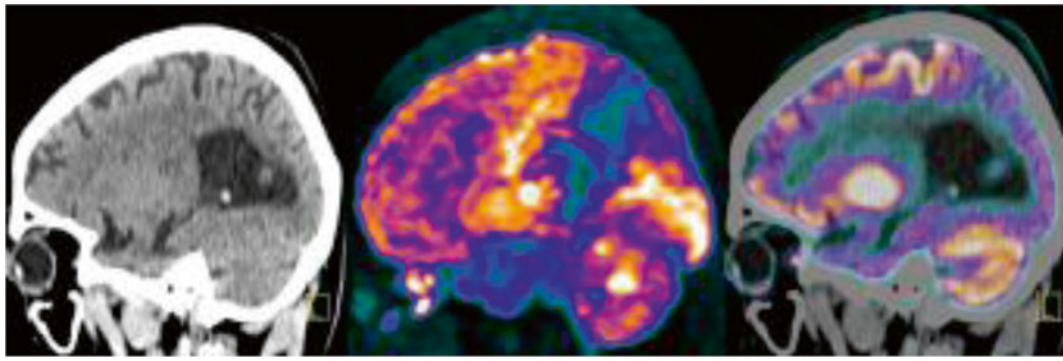

Fig. 7.3 Sagittal plain CT (*left*), sagittal MIP (*middle*), and sagittal fused ^{18} F-FDG PET-CT image (*right*) of a case of Alzheimer's dementia, typical metabolic pattern with parietotemporal hypometabolism and relatively preserved uptake in both visual and sensorimotor cortices, basal ganglia, thalami, and cerebellar hemispheres

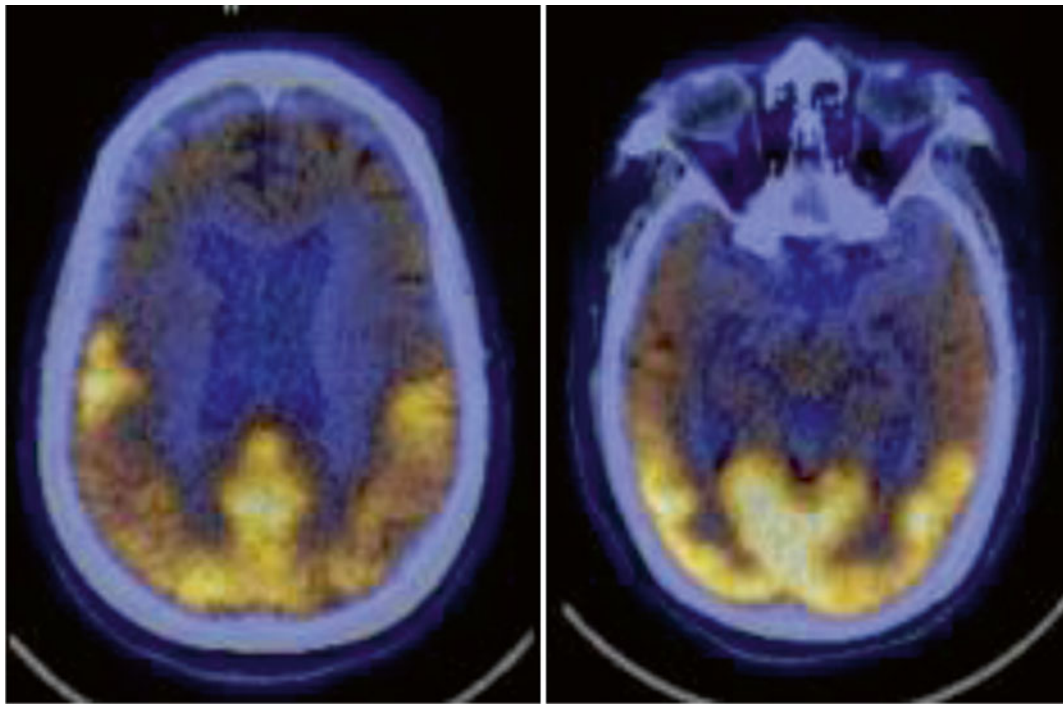

Fig. 7.4 Transaxial fused ^{18} F-FDG PET-CT image of a case of frontotemporal dementia (behavioral variant), classical metabolic pattern with frontal (*left*) and temporal (*right*) hypometabolism

diffuse Lewy body dementia (DLBD) from AD and FTD with nearly 80–87 % specificity and 83–90 % sensitivity in autopsy-validated studies. Further, a DAT agent can be used to differentiate AD from DLBD, while the basal ganglia would show normal DAT binding in AD; DAT binding would be reduced in DLBD.

^{18}F-FDG PET can be used to classify mild cognitive impairment (MCI) patients at risk for cognitive decline and progression to Alzheimer's based on the metabolic pattern of AD (Fig. 7.5). The pooled diagnostic accuracy of ^{18}F-FDG PET for differentiating AD from normal subjects was 93 %, in studies that used clinical assessment as

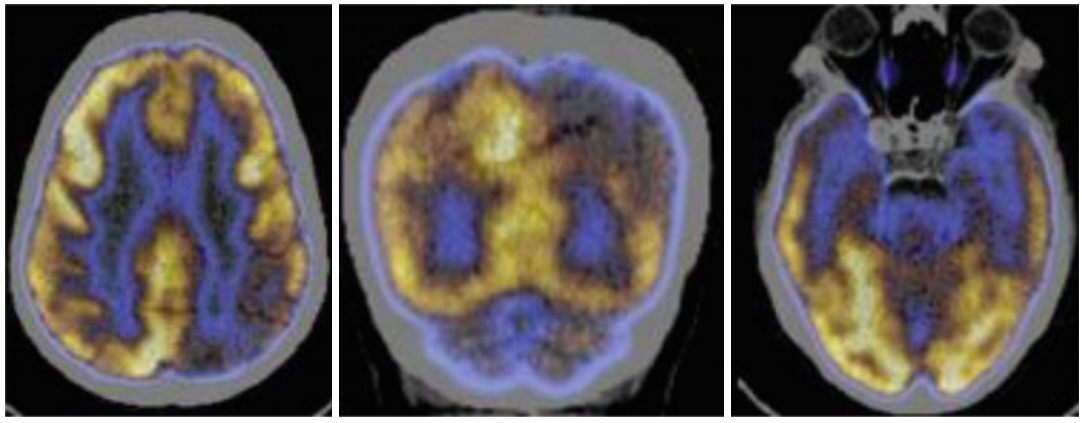

Fig. 7.5 Transaxial fused ^{18} F-FDG PET-CT image of a case of amnestic MCI, MMSE = 26, showing left parietal (*left*), precuneus (*middle*), and temporal (*right*) hypometabolism suggesting high likelihood for progression to AD

the reference standard. When neuropathological confirmation was used as the reference standard, sensitivity of ^{18}F-FDG PET for AD diagnosis was 94 %, and specificity was 73 % for patients presenting with other causes of dementia.

Amyloid Imaging

Amyloid beta deposition is a relatively early event on the path to AD. The amyloid cascade hypothesis states that overproduction or inability to remove â-amyloid results in amyloid deposition and subsequently in neurofibrillary tangles, inflammation, cell death, and cognitive impairment. PET tracers have been developed that bind to amyloid in vivo. The oldest of these is C-11 Pittsburgh (C-11 PiB) compound, which is limited by the presence of C-11 label with a short half-life (20 min). Thus, presently, F-18-labeled tracers like F-18 florbetapir have gained entry into markets worldwide. Appropriate use criteria for amyloid imaging have been defined, but this agent still lacks availability in India. The specific conditions when the use of amyloid is expected to make a difference have been defined as:

Patients with persistent or progressive unexplained MCI.

In patients satisfying core clinical criteria for possible AD but having an atypical clinical presentation or clinical course or an etiologically mixed presentation.

Patients with progressive dementia and an atypically early age of onset. Amyloid imaging can also be used to differentiate FTD from AD where it is expected that FTD patients would not show cortical binding of the amyloid agent.

Presently, amyloid agent is not being marketed in India.

Movement Disorders

The diagnosis of idiopathic Parkinson's disease (IPD) is primarily clinical. However, a common dilemma for doctors assessing patients in movement disorder clinics, especially early in the disease course, is that the main features of IPD are shared, at least in part, by several other disorders, which can be broadly classified into two categories, one which would not be associated with a dopaminergic deficit, like essential tremors, psychogenic Parkinsonism, and drug-induced Parkinsonism, and the second which share nigrostriatal degeneration as a common pathological feature with IPD and are called atypical Parkinsonian syndromes of multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal syndrome (CBS). The prognosis and management of each of these conditions differ significantly from that of IPD. The ability to reach a correct diagnosis and distinguish between the abovementioned entities is of clinical importance. In addition to the development and implementation of diagnostic clinical assessments,

Fig. 7.6 Maximum intensity projection (MIP) F-18 FDOPA images. *Left*—is of a normal subject showing the "rabbit-like" appearance of the basal ganglia with ears, head, and body. MIP (*right* image) is of a case of idiopathic Parkinson's disease showing loss of the rabbit's body (caudal putamen)

there is a need for objective markers to aid the physician in the diagnosis and differential diagnosis of IPD and the atypical syndromes. Thus, the most developed area in terms of providing an objective assessment is neuroimaging. Importantly, it can serve as a biomarker of trait, state, and rate of progression for Parkinson's disease.

Functional imaging using PET has a two-pronged approach for differential diagnosis of Parkinsonism:

I. Evaluating changes in striatal pharmacology by targeting various sites of the dopaminergic pathway, which can provide objective evidence of the presence of dopaminergic deficit and thus provide in vivo evidence of Parkinson's pathology. *Currently, the gold standard imaging technique with the highest resolution and power to differentiate between normal and abnormal nigrostriatal innervation is PET*. These tracers can be used to a limited extent to distinguish IPD from atypical Parkinsonian syndromes also.

II. Metabolic imaging using ^{18}F-FDG, which can be used to distinguish IPD from atypical Parkinsonian syndromes using a qualitative or quantitative image-based approach.
   (i) PET studies using presynaptic dopaminergic tracers have objectively demonstrated nigrostriatal nerve terminal loss in Parkinson's disease, even at very early or preclinical stages. Choice of tracer to use would depend on the stage of disease as during the very early or preclinical stages or in asymptomatic carriers of Parkin genes; a dopamine transporter (DAT) agent is preferable as DATs are downregulated quite early into the disease process, while amino acid decarboxylase (AADC) activity may be upregulated and vesicular monoamine transporter (VMAT) shows an intermediate effect. Classically, imaging reveals what is called a rabbit in the brain, with a body, head, and ears (Fig. 7.6-left), the head and body representing the rostral and caudal putamen, respectively, and the ears the caudate nuclei. Reductions are more severe in the posterior putamen and contralateral to the clinically most affected side; thus, the rabbit loses its body early, while the head and ears (caudate and rostral putamen uptake) are visualized till quite late into the disease process (Fig. 7.6-right). Nigrostriatal denervation is not specific for Parkinson's disease and is demonstrated in patients with atypical syndromes of MSA, PSP, and CBS. Imaging of the dopaminergic pathway is especially useful to differentiate dopamine deficiency state (Fig. 7.7) from non-dopaminergic deficient states like essential tremor and vascular, psychogenic, and drug-induced Parkinsonism, but may not be truly useful to differentiate IPD from the atypical subgroups. Dopaminergic imaging can also be used to assess graft viability following transplantation of embryonic dopaminergic tissue in vivo.

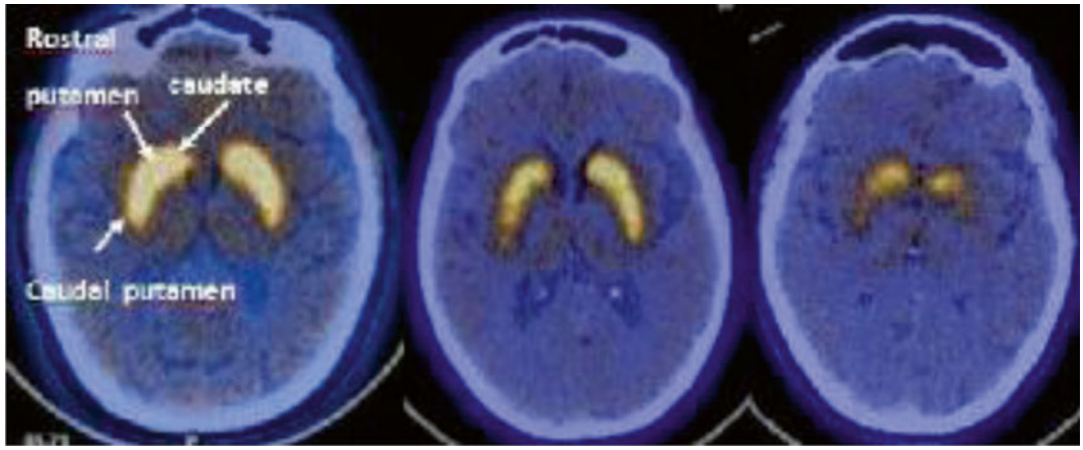

Fig. 7.7 Transaxial fused F-18 FDOPA PET-CT images at the striate level in a normal healthy volunteer (*left*) and in a patient with early IPD (*middle*) and in advanced IPD (*right*). In the patient with IPD (*middle*), there is an asymmetric loss of uptake of tracer, more pronounced in the caudal right putamen than in the caudate and rostral putamen. In advanced IPD (*right*), there is marked decrease in tracer uptake in both basal ganglia

(ii) Postsynaptic D2 receptor imaging, on the other hand, can be used to differentiate IPD from the atypical group as D2 receptor availability is normal or upregulated in untreated IPD (as a compensatory response to the decrease in presynaptic dopamine), whereas in the atypical groups there is a loss of D2 receptors (GABAergic spiny interneuron loss), which can be effectively imaged using tracers like C-11 raclopride and F-18 fallypride. In treated or long-standing IPD, D2 binding normalizes or is only mildly reduced. This is in contrast to MSA or PSP where a significant reduction in D2 receptor binding is seen, and thus a 100 % separation is achieved. However, D2 receptor imaging would not be useful to differentiate MSA from PSP or these two from CBGD.

Thus, depending on the question to be answered, the agent that could best be used for:

- Early identification of a dopaminergic deficit states—*DAT agent like F-18 FP-CIT*
- Establishing IPD, MSA, PSP, and CBS (dopaminergic deficiency)—*F-18 FP-CIT, F-18 FDOPA, and F-18 AV133*
- Differentiate IPD from MSA, PSP, or CBS—*D2 agent like F-18 fallypride*
- Differentiating MSA from PSP or CBS—*none of these would help (^{18}F-FDG PET is useful)*

(iii) Metabolic imaging with ^{18}F-FDG in Parkinsonism

In addition to changes in striatal pharmacology (receptor, transporter, or enzyme status), PET can be used to quantify resting changes in regional glucose utilization using ^{18}F-FDG. In early IPD, striatal metabolic activity is increased in the lentiform nucleus contralateral to the affected limb. A number of studies using ^{18}F-FDG have described characteristic patterns of glucose metabolism in patients with IPD (Fig. 7.8-right), MSA (Fig. 7.9), PSP (Fig. 7.10), and CBS (Fig. 7.11). Based on these patterns, visual analysis and computer-supported reading using statistical parametric mapping (SPM) have been useful for differential diagnosis of IPD from MSA and PSP (Table 7.2).

Others

While the initial studies of PET were in stroke with interesting applications, but as of date it has not found great utility in day-to-day neurology practice.

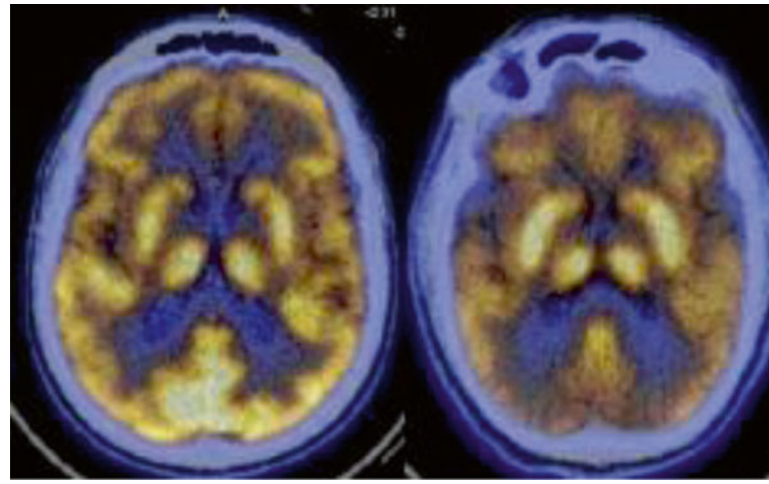

Fig. 7.8 Transaxial fused ^{18}F-FDG brain PET-CT image of a normal subject (*left*) and in idiopathic Parkinson's disease (*right*), hypermetabolism is noted in basal ganglia (caudally) with parieto-occipital hypometabolism; this is the typical metabolic pattern of IPD

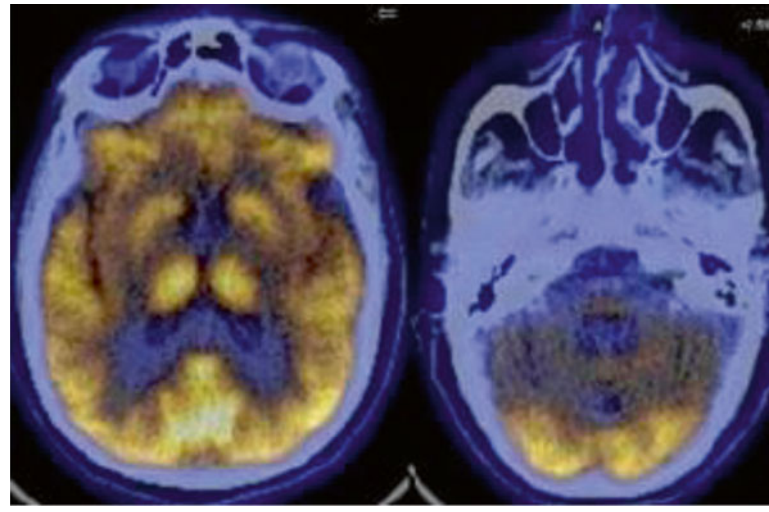

Fig. 7.9 Transaxial fused F-18-FDG PET-CT image (*left*) of a case of MSA-C; hypometabolism is noted in both basal ganglia posteriorly and in both cerebellar hemispheres (*right*)

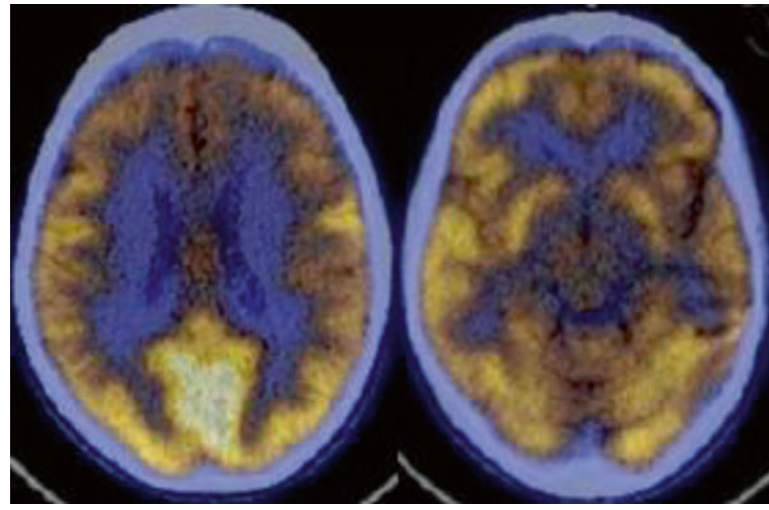

Fig. 7.10 Transaxial fused F-18-FDG PET-CT image of a case of PSP; hypometabolism is noted in both frontal and anterior cingulate cortices (*left*) and in both basal ganglia and midbrain (*right*)

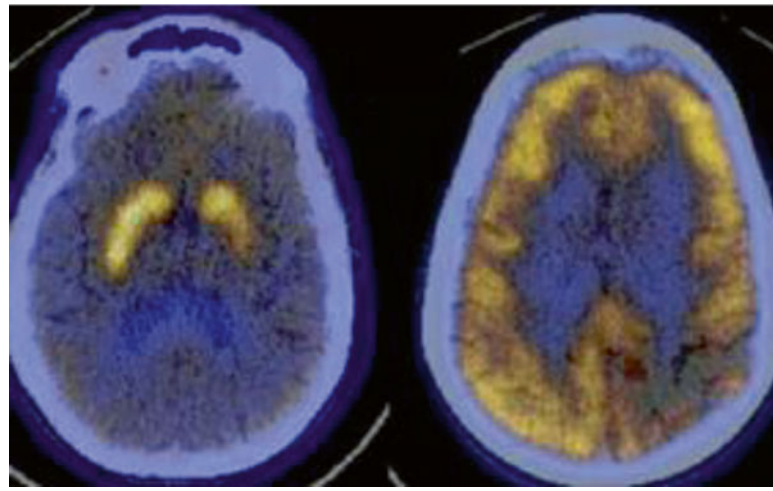

Fig. 7.11 Transaxial fused F-18-FDOPA image (*left*) showing decreased tracer uptake in caudal left putamen in a case of CBS symptomatic on the right side. Transaxial fused ^{18}F-FDG PET-CT image (*right*) of the same case of CBS; hypometabolism is noted in the left parietal cortices

Table 7.2 An overview of all functional markers that can be used for the diagnosis and differential diagnosis of Parkinsonian syndromes

Disease	Presynaptic markers (DAT, FDOPA, VMAT)	Postsynaptic markers (D2 receptor targets)	Metabolic patterns (F-18 FDG)
Idiopathic Parkinson's disease	Decreased asymmetrically with rostrocaudal gradient	Normal or upregulated	Pallidothalamic and pontine hypermetabolism, parieto-occipital hypometabolism
Multiple system atrophy	Decreased involving both caudate and putamen	Decreased	Hypometabolism in both basal ganglia marked posteriorly ± cerebellar hypometabolism
Progressive supranuclear palsy	Decreased involving both caudate and putamen	Decreased	Hypometabolism in both basal ganglia, midbrain, and anterior cingulated cortices
Corticobasal Syndrome	Decreased posteriorly opposite to clinically affected side	Decreased	Hypometabolism in the basal ganglia and parietal cortices opposite to the clinically affected side

Another interesting application of PET is in patients with paraneoplastic syndromes (PNS). PNS represent rare symptom complexes resulting from the ability of tumor cells to disrupt the homeostatic processes of various body systems. Suspecting and investigating PNS are crucial as up to 80 % of patients present with PNS before there is any other indication of malignancy. A PET scan and regular surveillance may reveal occult malignancies better than CT or MRI (Fig. 7.12). Neuromodulatory therapies and treatment of the underlying malignancy remain the best management options in the patients being evaluated for primary malignancies. ^{18}F-FDG PET is a useful whole-body screening modality for localizing the primary site in these patients.

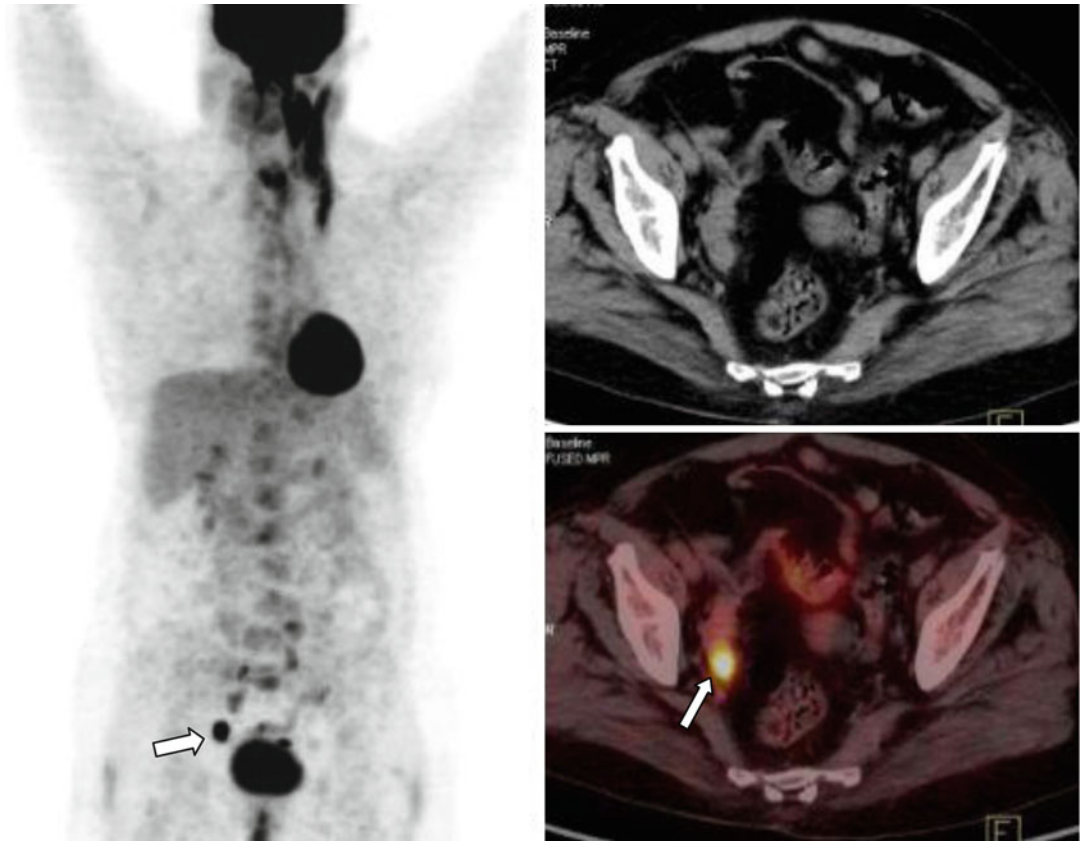

Fig. 7.12 A 66-year-old female presenting with acute onset of cerebellar signs. A PNS was suspected. The whole-body FDG PET-CT revealed a hypermetabolic soft tissue density mass in the right adnexal region which was confirmed to be an Ovarian neoplasm on biopsy (*arrows*)

For Further Reading

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