Review Article

Positron emission tomography in neurological diseases

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Positron emission tomography (PET) is the study of human physiology by electronic detection of positron-emitting radiopharmaceuticals. It is one of the noninvasive technologies that can measure the metabolic and functional activity of living tissue. Positron emission tomography finds its clinical applications in broadly three specialties – oncology, cardiology, and neurology. The current review focuses on its indications in neurological diseases. Recently published literature on the use of PET in neurology has been thoroughly analyzed. Several reports regarding the usage of PET in epilepsy, stroke, dementia, and movement disorders are available. Positron emission tomography does not appear to be useful as a primary or sole imaging technique in these conditions. On the other hand, it is useful in very specific situations, which have been elaborated in the review. It is also noteworthy that PET is complementary to the computed tomography/magnetic resonance imaging findings and data obtained from combining these modalities can be valuable in situations such as localization of the epileptogenic focus in cases of refractory epilepsy or for prediction of the outcome after thrombolysis in acute ischemic stroke. The major handicaps in widespread use of PET appear to be its lack of availability and its relatively high cost. Nevertheless, a review such as this would be helpful in judiciously selecting those patients who would benefit from undergoing a PET scan, at a time when PET imaging facility is likely to be available soon in the Indian private sector.

Key Words: Clinical applications, neurological diseases, positron emission tomography

Positron emission tomography (PET) is the study and visualization of human physiology by electronic detection of short-lived positron-emitting radiopharmaceuticals. It is one of the noninvasive technologies that can routinely and quantitatively measure metabolic, biochemical, and functional activity in living tissue. It assesses changes in the function, circulation, and metabolism of body organs. It should be noted, however, that other technologies such as SPECT, functional magnetic resonance imaging (MRI) and MR spectroscopy are also capable of measuring the metabolic and functional activity *in vivo*. Unlike MRI or CT (Computed Tomography) imaging, which primarily provide images of organ anatomy, PET measures chemical changes that occur before visible signs of disease are present on CT and MRI images.

Overview of PET procedure

The basic steps of PET imaging involve (i) 4-hour fasting (the rule may be relaxed for diabetics), (ii) administration of FDG (Fluorodeoxyglucose) (dose is based on body weight and the usual dose is 10 mCi) as an intravenous injection after the patient relaxes for 5 min in a dimly lit room, (iii) patient rests for 40 min after the injection, with eyes open and ears unplugged in a similar environment, (iv) imaging is started no sooner than 40 min after the injection and is over in 15 min. The dose of radionuclide injected is minute and does not pose any significant hazard. Various isotopes are used depending upon the brain region and function studied. Table 1 lists the important tracers used in neurological diseases.[1]

Clinical applications

Positron emission tomography is useful in three broad categories of diseases:

1. *Oncology*: (a) It is helpful in differentiating malignant from benign tumors; (b) It helps in locating the best site for biopsying a suspected tumor; (c) It is useful in monitoring the effects of therapy (either radiation or chemotherapy or both); (d) It is also able to detect the site(s) of recurrent disease and differentiate it from radiation tissue necrosis; (e) The most important application of PET is its ability to detect cancers of breast, colon, lung, etc., at a stage when the conventional imaging modalities fail to do so.

2. *Cardiology*: (a) Positron emission tomography can be used to assess the extent of cardiovascular disease, especially coro-

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Table 1: List of common positron emission tomography radioisotope tracers used in the evaluation of neurological disorders

Application	Radioisotope tracer used
Activated microglia	^{11}C(R)-PK11195
Cellular amino acid uptake	^{11}C-Methionine
Central benzodiazepine binding	^{11}C-Flumazenil
Cerebral blood flow	$H_2{}^{15}O$
Dopamine storage	^{18}F-6-Fluorodopa (^{18}F-dopa)
Dopamine D_1 receptor binding	^{11}C-SCH23390
Dopamine D_2 receptor binding	^{11}C-Raclopride
Glucose metabolism	^{18}F-2-deoxyglucose (^{18}FDG)
Inflammatory response	^{55}Cobalt
Monoamine oxidase A binding	^{11}C-Deprenyl
Opiate receptor binding	^{11}C-Diprenorphine
Opiate receptor binding	^{11}C-carfentanil
Opiate receptor binding	^{18}F-cyclofoxy
Oxygen metabolism	$^{15}O_2$

nary artery disease, and is particularly centered on the detection of viable/hibernating myocardium; (b) Positron emission tomography helps in identifying patients who are likely to benefit from revascularization procedures such as stenting and bypass surgeries.

3. *Neurology*: Positron emission tomography is useful in diagnosis, planning treatment and predicting outcomes in various neurological diseases. Each of them will now be briefly discussed.

Epilepsy

Diagnosis

Presurgical evaluation and localization of epileptogenic foci. Interictal PET shows decreased glucose metabolism and blood flow in the epileptogenic focus. Magnetic resonance imaging, PET, and ictal SPECT play important roles in presurgical localization of epileptic foci in patients with refractory epilepsy. In a comparative study of these methods, the rates of lesion localization by MR, ictal SPECT, and interictal ^{18}F-2-deoxyglucose (^{18}FDG) PET was found to be 60, 70, and 78%, respectively.[2] However, the sensitivity and specificity of postictal SPECT in localizing epileptogenic foci can be significantly increased by subtraction SPECT co-registered to MRI (SISCOM).[3] This shows the superiority of ^{18}FDG-PET over SPECT and MR in presurgical evaluation of patients. Though it has been argued that invasive procedures such as ictal electrocorticography and subdural electrodes might identify the epileptogenic foci in patients with normal PET scans,[4] PET obviates the need for invasive electrophysiological monitoring in most instances.[5] However, a combination of invasive monitoring and PET might be able to more precisely localize the epileptogenic lesion.

Temporal lobe epilepsy (*TLE*). Positron emission tomography with [^{11}C]deuterium-deprenyl is useful in the identification of the epileptogenic temporal lobes in patients with TLE and it correctly identifies the side with epileptogenic foci in most cases.[6] Seizure lateralization with qualitative MR is inferior to qualitative PET (QPET). However, quantitative MRI with hippocampal volumetric assessment was found to be more sensitive than QPET in lateralizing the side of TLE.[7] It should be noted that the area with abnormal cerebral blood flow and metabolism seen on PET is considerably larger than the actual structural abnormality, possibly due to reduced synaptic inhibition or deafferentation of neighboring neurons in areas of epileptic propagation.[8] Therefore, false localizations may occur, the probability of which can be lessened by using quantitative rather than qualitative assessment of regional cerebral metabolism. Overall, for epileptogenic foci ^{18}FDG-PET may be more suitable as a lateralizing rather than localizing tool.

Routine diagnosis of epilepsy. Positron emission tomography is more sensitive than MRI in routine evaluation of epilepsy, as abnormalities on PET are detected in about 40% of those patients who have supposedly 'normal' looking brains on MRI.[9] Positron emission tomography is also useful in excluding nonepileptic seizures and idiopathic generalized epilepsies. However, the same authors reported EEG to be more sensitive than PET.[9] This again highlights the fact that PET cannot be used as a sole imaging modality in evaluating epilepsy and has to be combined with EEG.

Treatment and outcome

1. Identification of nonresected epileptic cortex in patients with previously failed neocortical epilepsy surgery is possible with PET using alpha-[^{11}C]methyl-L-tryptophan (AMT).[10] Epileptogenic areas show increased tracer uptake. Proper timing of the scan can also assist in planning reoperation.

2. *Prediction of postoperative outcome*: Interictal metabolic pattern on PET using ^{18}FDG reliably predicts the seizure outcome at 2 years after surgery in patients with medial TLE.[11] In a comparison between the abilities of MR and PET to predict the postoperative outcome, MR identified 83% of those with good outcomes as compared to 71% identified by PET.[12] Thus, MR sensitivity exceeded that of PET. However, when MR and PET were combined, they detected 95% of the patients with good outcome. This shows that PET is not a substitute for MR; rather they play complementary roles.

Stroke

Identification of viable penumbra tissue in acute ischemic stroke

It is vital to distinguish irreversibly damaged tissue from viable penumbra tissue, as irreversibly damaged areas cannot benefit from reperfusion therapy (thrombolysis). Central benzodiazepine receptor ligands, such as [^{11}C]flumazenil

(FMZ), are markers of neuronal integrity and therefore are useful in the differentiation of functionally and morphologically damaged tissue early in ischemic stroke. Flumazenil PET distinguishes between irreversibly damaged and viable penumbra tissue early after acute stroke.[13]

Differentiation between recent and old stroke in patients with recurrent ischemic strokes

Cobalt 55 PET is able to achieve this differentiation.[14] Recently infarcted areas, less than 2-month old, have a high ^{55}Cobalt (^{55}Co) uptake ratio, whereas infarcts of 6 months to 1 year have an uptake ratio comparable to normal brain tissue. The evolution in ^{55}Co uptake ratios with time can be explained by the dynamics of the inflammatory response within the infarct core.

Predicting the probability of cortical infarction in acute ischemic stroke

[^{11}C]flumazenil-PET and diffusion-weighted MRI (DWI) were compared with respect to the probability to predict cortical infarction in early ischemic stroke. They were found to be comparable in this aspect; however, the FMZ-PET carried a lower probability of false-positive prediction.[15] The discrepancy in predictive probability could be related to the fundamental difference in the measured variables: benzodiazepine receptor activity (measured by PET) is a reliable marker of neuronal integrity in the cortex, and movement of water molecules in the extracellular space (measured by DWI) might be a more variable indicator of tissue damage.

Prediction of engraftment of neuronal implantation in chronic stroke

Recently, PET with ^{18}F-FDG was used to map the metabolic brain response to neuronal cell implantation in the first human neuroimplantation trial for stroke. Serial FDG-PET demonstrated a relationship between relative regional metabolic changes and clinical performance measures. These findings were suggestive of improved local cellular function or engraftment of implanted cells in some patients.[16]

Demonstration of diaschisis

Several types of diaschisis (effect of acute stroke in a region on remote brain areas) can be demonstrated by PET.[17] They reflect different pathophysiological changes in supratentorial infarcts.

Evaluation of late-onset seizures in patients with old stroke

It is commonly believed that poststroke seizures occur due to gliotic changes or scarring of cerebral cortex. However, PET evaluation using ^{55}Co as a tracer in patients with old stroke presenting with late-onset epilepsy showed that in many cases, epilepsy is the manifestation of recurrent strokes in the same vascular territory.[18] Increased uptake of ^{55}Co in the old infarct core in addition to the border zones suggests a reinfarction in the same region.

Dementia

Detection of progressive dementia

^{18}Fluorodeoxyglucose-PET has a sensitivity of 93% and specificity of 76% in identifying progressive dementia in patients undergoing evaluation for cognitive impairment.[19] Among patients with neuropathologically based diagnoses of Alzheimer's disease (AD), the sensitivity and specificity of PET increased to 94 and 73%, respectively. A negative PET virtually rules out a pathologic progression of cognitive impairment.

Differentiation between AD and vascular dementia

In mild or atypical cases of AD, the differential diagnosis to other dementing diseases, such as vascular dementia (VaD), may pose a difficult problem. ^{18}Fluorodeoxyglucose-PET shows a typical metabolic pattern in AD: hypometabolism in temporoparietal and frontal association areas, but relative recessing of primary cortical areas, basal ganglia and cerebellum. In VaD, a different pattern characterized by scattered areas with reduction of regional cerebral glucose metabolism extending over cortical and subcortical structures is observed.[20]

Differentiation between AD and dementia with Lewy bodies (DLB)

Regional cerebral metabolic rate of glucose has been studied using ^{18}FDG-PET in patients with dementia. In DLB, the regional cerebral glucose metabolism is reduced in temporoparieto-occipito association cortices and the cerebellar hemispheres, as against AD, where medial temporal and cingulate are affected.[21]

Monitoring of effect of treatment with cholinesterase inhibitors in AD

Positron emission tomography evaluation before and after therapy with donepezil or rivastigmine is helpful in assessing the treatment benefits.

Early diagnosis of AD

Neuropathological and neuroimaging data suggest that amyloid accumulation precedes the clinical onset of AD. Disease-modifying agents would have to be used early to alter the course of AD. Therefore, preclinical diagnosis is necessary. Positron emission tomography shows abnormalities in the early stage of AD and it may even aid in preclinical diagnosis. It is superior to neuropsychological testing for diagnosis of dementia in very early stages.[22] Neuropsychological tests have mostly been standardized to the Western population, and may not apply to the Indian population, especially noneducated peo-

ple, unless serial testing is performed. Positron emission tomography may be especially useful in this situation, as it gives objective measures of preclinical disease state. In addition, PET may be used for screening of AD in high-risk groups of asymptomatic patients, such as in persons homozygous for epsilon 4 allele for apolipoprotein E.[23] Early diagnosis of AD would lead to early institution of treatment and even prevention in some cases.

In vivo *amyloid imaging in AD*

The prospect of *in vivo* imaging of amyloid peptide leading to the diagnosis of AD in preclinical and prodromal phases of the disease appears very promising.[24]

Movement disorders

Parkinson's disease (PD)

Positron emission tomography has several proven or promising indications in PD: (a) Diagnosis of PD in early stages: Functional brain imaging with PET and the radiotracer ^{18}Fluorodopa (FDOPA) can quantify the deficiency of dopamine synthesis and storage within presynaptic striatal nerve terminals. Therefore, FDOPA-PET allows the diagnosis of PD in early disease stages;[25] (b) Diagnosis of PD in preclinical stages in persons at risk for the disorder: ^{18}FDOPA-PET can differentiate patients with early PD from normal. Borderline low-normal subjects have slightly low-fluorodopa F 18 uptake throughout the striatum, whereas patients with early PD have low-fluorodopa F 18 uptake in one putamen with preserved uptake in the caudate nucleus;[26] (c) Differentiation of PD with other movement disorders such as essential tremors; (d) Differentiation between PD and striatonigral degeneration (SND) is possible by PET and carbon-11 labeled SCH23390.[27] The SND patients showed mean 12, 21, and 31% declines in the ratios of radioactivity in the caudate, anterior putamen and posterior putamen compared with that in the occipital cortex. These ratios were not significantly altered in the PD patients. Parkinson's disease is characterized by loss of dopaminergic neurons in the pars compacta of the substantia nigra. ^{18}Fluorodopa-PET in PD demonstrates these changes in putamen followed by caudate nucleus.[28]; (e) To examine the dopaminergic deficit and its relationship to motor performance: in untreated PD, there is increased density of D_2 binding sites, while in chronically treated PD with motor fluctuations, D_2 receptor density is reduced;[29] (f) Follow up of disease progression; (g) Assessment of medical and surgical therapies with possible neuroprotective strategies; (h) Assessment of graft viability after embryonic dopamine cell implantation: PET imaging with ^{18}FDOPA was undertaken before and 1 year after transplantation. A significant increase in FDOPA uptake in the putamen of the group receiving implants was observed as compared to the placebo surgery patients.[30]

Dystonia

^{18}Fluorodeoxyglucose-PET studies have shown a decreased regional cerebral glucose metabolic rate in caudate and lentiform nucleus and in the frontal projection field of the mediodorsal thalamic nucleus as compared to the normal controls.[31] Global cerebral glucose metabolism was, however, unaltered when compared to normal controls.

Huntington's disease (HD)

Preclinical detection of HD is possible by demonstrating reduced caudate glucose utilization in persons at high risk for the disorder as detected by DNA studies.[32] Positron emission tomography studies of caudate glucose utilization may help to confirm results of DNA studies in some persons, and may provide an opportunity to detect when DNA results may be incorrect due to recombination.

Brain tumors

Primary brain tumors account for 1–2% of all malignancies. Computed Tomography or MRI is often the initial imaging performed in patients suspected to have brain tumor. These modalities provide excellent information of the lesion anatomy and extent. However, they may not be able to differentiate benign from malignant lesions. In addition, CT or MRI may not be able to differentiate between tumor recurrence and radiation necrosis, as both may show contrast enhancement that could persist for months. This is where PET scores over them.

Differentiation between tumor recurrence and radiation necrosis

Differentiating radiation necrosis from recurrent tumor is a diagnostic challenge; however, this has important implications for the patient's management. Even though the first results were published 20 years ago, the total number of case studies using FDG-PET in this indication remains limited. As a general rule, suspicious lesions on MR imaging that show increased FDG uptake (i.e., uptake equal to or greater than that in a normal cortex) are likely to represent tumor recurrence.[33] Although false-positive results may occur, specificity is usually high in routine clinical practice. Co-registration with MRI surely improves the diagnostic performances of FDG-PET because it helps delineate the suspicious area.

Diagnostic assessment of cerebral gliomas

Gliomas account for about 45–50% of primary brain tumors. In a recent study, it was found that MRI yielded a sensitivity of 96% for the detection of tumor tissue but a specificity of only 53%, and combined use of MRI and O-(2-[^{18}F]fluoroethyl)-l-tyrosine (FET) PET yielded a sensitivity of 93% and a specificity of 94%.[34] This proves that the combined use of MRI and FET PET in patients with cerebral gliomas significantly improves the identification of cellular

glioma tissue and allows definite histological diagnosis.

Grading of brain tumors

2-[^{18}F]fluoroethyl)-l-tyrosine PET can differentiate between malignant tumors and benign lesions of the brain. In addition, high- and low-grade brain tumors exhibit different uptake kinetics of FET.[35] In another study, [^{18}F] 3¢-deoxy-3¢-fluorothymidine (FLT) PET was found to be useful for evaluating tumor grade and cellular proliferation in brain tumors.[36] However, it did not appear to be sufficiently useful for differentiating tumors from nontumorous lesions. Prediction of tumor grade has implications on patients' survival. In a study, 94% of patients with low-uptake survived for >1 year and 19% survived for >5 years. Only 29% of patients with high-uptake survived for >1 year, and none survived for >5 years.[37]

Miscellaneous

Headache

Positron emission tomography studies in patients with migraine have shown an increased cerebral blood flow in midline brainstem structures during the headache phase, which persisted even after treatment with sumatriptan.[38] This could reflect the activity of a presumed migraine center in the brainstem.

Chronic fatigue syndrome (CFS)

^{18}Fluorodeoxyglucose-PET studies in patients with CFS show hypometabolism in the right mediofrontal cortex and brainstem. Brainstem hypometabolism seems to be a specific marker for *in vivo* diagnosis of CFS.[39]

Encephalitis

Rasmussen's encephalitis. Positron emission tomography shows a diffuse, unilateral cerebral hypometabolism that correlates with the regions of cerebral atrophy on MR images. Although MR imaging data alone are sufficient to suggest a diagnosis of Rasmussen's encephalitis (RE) in many cases, correlation with ^{18}FDG-PET data increases the diagnostic confidence and allows the unequivocal identification of the affected cerebral hemisphere in patients whose MR imaging findings are subtle or distributed bilaterally.[40] Moreover, PET demonstrates the features of subcortical involvement much earlier than that of MR imaging.[41] It should be mentioned, however, that despite early pathologic confirmation of RE, there are no definite structural or functional imaging changes on PET or MRI until 3 years after symptom onset.[41] Positron emission tomography imaging can be used to study the neuroinflammation in RE *in vivo*, aid in the selection of appropriate biopsy sites and assess the response to anti-inflammatory therapeutic agents.[42]

Paraneoplastic encephalitis (*PNE*). Traditionally, MR imaging is performed to aid in the diagnosis of PNE. However, ^{18}FDG-PET imaging has shown positive findings in a case of PNE, associated with cystic teratoma, where the MR imaging was negative.[43] Therefore, PET may be superior to MR imaging in some cases of PNE.

Multiple sclerosis

^{18}Fluorodeoxyglucose-PET studies in patients with MS show features of widespread cerebral dysfunction including cortical gray matter. The quantitative cerebral abnormalities detected by FDG-PET may serve as a marker of disease activity in understanding the pathophysiological expression and therapeutic response of MS.[44] Fatigue is a common symptom in MS. Positron emission tomography studies have suggested that fatigue in MS is associated with frontal cortex and basal ganglia dysfunction that could result from demyelination of the frontal white matter.[45] ^{55}Cobalt-PET has been used as a tool for assessing the disease progression rate in relapsing progressive-MS. These findings correlate well with MRI findings.[46]

Limitations of PET

The major limitation of PET is its lack of easy availability. At present, it is mostly available in the developed countries and predominantly in larger research institutes. In India, PET is largely unavailable in most hospitals. However, PET machines are available for research purposes in DRDO, New Delhi and Bhabha Atomic Research Center (BARC), Parel, Trombay, Mumbai. In the hospital setting, India has only one dedicated PET camera at the Tata Memorial Hospital and three coincidence gamma PET cameras (which may not play any role in brain studies) at the Hinduja Hospital, Jaslok Hospital and Bombay Hospital.[47] The first PET-CT scan in South Asia costing INR 60 crores has been installed at Apollo Hospitals, Jubilee Hills at Hyderabad and it is fully functional.[48] Another associated limitation is its high cost. It is likely to cost 25 000 INR (555 USD) per study.[42]

The radiation hazard posed by PET is negligible and is equivalent to the hazard posed by CT scan.[49] The radioisotopes do not stay in the body for long due to their short half-lives; therefore there is no need to avoid interacting with other people. Pregnant and lactating mothers, however, should avoid undergoing PET scanning.

Technical limitations include a relatively high incidence of false-positive reports, which reduces its specificity. Moreover, specially trained personnel are required to interpret the reports. A cyclotron capable of generating the necessary radioisotopes is required in the vicinity of the PET scanner as most of these isotopes have a very short half-life.

Conclusions

Positron emission tomography is an important, though ex-

pensive, neuroimaging tool available to study various neurological diseases. Its exact role, however, in these disorders is yet to be defined. Based on the published research, it appears to play a definite role in the localization of epileptogenic foci in patients with medically refractory epilepsy. It is also useful in identifying abnormalities in patients with routine epilepsies and normal MR. The most important use of PET in acute stroke is to identify the salvageable part of the ischemic penumbra, thereby defining the role of reperfusion. The other major use is in identifying recurrent strokes in patients with old strokes in the same vascular territories. Positron emission tomography would be primarily useful for the diagnosis of AD in the very early phase including in asymptomatic persons. It also helps in differential diagnosis of dementia. Positron emission tomography could also be used for preclinical diagnosis of PD and differentiating it from essential tremors or SND. On account of its high costs and poor accessibility, PET should be judiciously used.

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