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Recent trends in Molecular Imaging : PET/CT in Neurology

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SUMMARY

PET/CT is an important molecular imaging technique for the assessment of neurological disorders. The most widely used radiopharmaceutical for both clinical and research purposes is [18F] 2-fluoro-2-deoxy-D-glucose (FDG). It is extensively used owing to its favourable physical characteristics. It enables depiction of cerebral glucose metabolism, and has thus been used to study various pathological states. Despite this, FDG has its own limitations. This is owing to its limited specificity and high cortical uptake. This has paved the way for the development of several non-FDG PET radiopharmaceuticals. We present the insights gained at our institution, using these radiotracers in the assessment of neurological disease. Our study shows that the use of FDG and non-FDG novel PET radiopharmaceuticals facilitates the early diagnosis, delineation of extent, prognostication and monitoring of therapeutic response in several neuropathological states.

Key Words : Molecular imaging, PET/CT, Neurological disorders

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Introduction

The first oncological application of PET was in the assessment of brain tumors (1). In general, PET/CT using FDG has gained widespread acceptance in tumor evaluation owing to its ability to detect tumors and define their extent, provide information that aids planning of radiotherapy and operative interventions, show response to treatment, and detect tumor recurrence. FDG has been aptly called the molecule of the millennium owing to its profound impact on oncological imaging. However, FDG may not be an ideal imaging agent for brain tumors as there is a high physiological glucose uptake in normal brain parenchyma, glucose being an obligatory energy substrate for brain. This leads to intense radiotracer uptake in normal brain tissue (2), and, as a result, low grade tumors, small tumors, and tumors with early recurrence may go undetected. Moreover, FDG uptake is relatively nonspecific and is seen to occur in inflammatory and granulomatous tissues also (3).

A host of non-FDG PET radiotracers with oncological applications have been developed. These include radiotracers for amino acid synthesis, Deoxyribonucleic acid (DNA) synthesis, lipid synthesis, hypoxia, angiogenesis, and peptide receptors.

Each of these has their inherent strengths and limitations, a detailed understanding of which is a pre-requisite to their optimal utilization.

One of the most important neurological application of PET imaging is in the work-up of the dementia patient (4). It serves as a useful aid to enable an accurate diagnosis as early in the course of the disease as possible. It also aids in differentiating the different forms of dementia on the basis of pattern of FDG uptake in different parts of the brain parenchyma. Further, it facilitates the determination of the course and severity of the disease. FDG PET/CT is also proving useful in the detection of cases with MCI (mild cognitive impairment). The early diagnosis and response to therapeutic intervention is an area of intense research today.

Movement disorders, namely Parkinson's Disease and Parkinsonian Syndromes can be assessed using PET/CT. Based on the differential pattern of uptake of FDG in various disorders, the various subgroups of movement disorders can be distinguished. Further, PET imaging with 18F-fluorodopa has been performed to evaluate the presynaptic dopaminergic function, and has shown abnormalities in the nigro-striatal projection (5). 18F-fluorodopa studies have been used in early diagnosis, investigation of clinical course and the effects of therapy in patients with movement disorder. Imaging with postsynaptic dopamine receptor tracers has also been undertaken, to assess the pathogenesis and course of the disease.

Other important areas where PET/CT plays an important role is cerebrovascular disease (haemorrhafic or ischemic), seizures, brain trauma etc.

Material and Methods

The study comprised of 286 patients with neurological disease. Of these, there were 117 subjects with dementia 104 subjects with movement disorders and 65 subjects with brain tumors. All patients underwent an FDG PET scan. Of the 286 patients, 153 number of cases further underwent scanning using non-FDG novel radiotracers. All participants provided written informed consent.

For the FDG PET study, all subjects were fasting for at least 4 hours prior to the study. The study was performed in a resting state with eyes closed. It was performed on a Discovery STE 16(GE) camera. A dose of 370 MBq of FDG was injected intravenously and a brain scan was obtained after an interval of 60 minutes, with patient in supine position and head immobilized in a head rest. An initial scout was followed by a low dose CT acquisition. This was followed by a static 20 minute single bed position 3-dimensional emission scan. Reconstructed data was viewed on a Xeleris work-station. Data acquisition was performed along similar lines for other non-FDG PET tracers, with modification of dose and post-injection waiting period depending on the individual radiopharmaceutical, eg. 550-740 MBq of 11C-methionine with 20 minute delay post-injection.

Data analysis was performed by visual image interpretation using plain PET, CT and fused PET/CT images. Semiquantitative assessment using SUVmax was also performed in those cases where a lesion was localizable. SUV (standardized uptake value) is a semiquantitative numerical value which normalizes the lesion uptake to injected dose per unit body weight. The same procedure was performed for both FDG and non-FDG PET procedures.

Results

The patients evaluated on PET/CT could be broadly categorized into 3 large subsets : brain tumor, cases of dementia and movement disorder.

Brain Tumors :

A total of 97 patients with intraparenchymal brain tumor was assessed. Of these, histological confirmation was possible in 65 cases. Of these 65 subjects with brain tumor, there were 18 newly diagnosed cases and 47 previously treated cases. FDG PET/CT was performed in all cases, while 11C-methionine scan was performed in 45 cases, F-DOPA (3,4-dihydroxy-6-18F-fluoro-L-phenylalanine) scan was performed in 20 cases, FLT (18-fluorothymidine) in 19 cases, FMISO (18F-misonidazole) scan in 3 cases and FET (O-(2-[18F]fluoroethyl)-l-tyrosine) in 2 cases.

11C-methionine was found to be more efficacious than FDG PET/CT both for the primary detection of tumor and delineation of its extent (fig.1). It was useful in distinguishing tumorous from

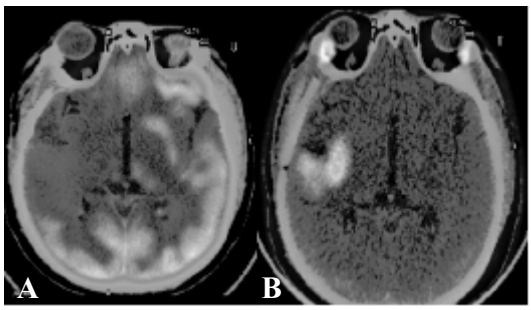

Fig.1 : A post-operative case of grade II glioma. FDG PET/CT image (A) shows no area of increased uptake at the operative site s/o negative study. However, 11C-methionine scan (B) clearly shows recurrence in the right temporal region (arrow).

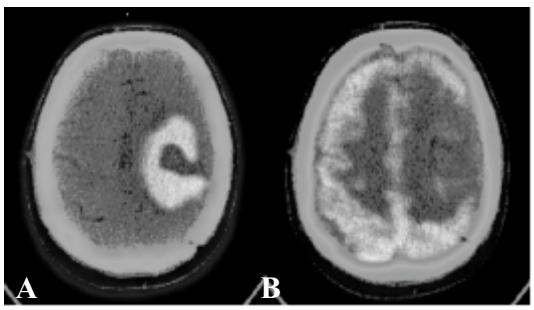

Fig.2 : A post-operative case of recurrent glioma. Lesion delineation is superior on F-DOPA PET/CT image (A) compared to the FDG PET/CT image (B).

non-tumorous lesions. It showed selective uptake in neoplastic tissue, and was thus useful in assessing the size and margins of the lesion. This was applicable both for primary tumors and post-treatment cases as well. Low grade gliomas were also better depicted on 11C-methionine PET/CT. In case of recurrent brain tumors, it was superior to FDG not just in the delineation of the area of recurrence, but also in the detection of secondary deposits. Also, interobserver variability in interpretation was less on 11C-methionine compared to FDG.

F-DOPA was extremely sensitive in picking up both primary and recurrent lesions (fig.2). It scored over FDG in the evaluation of all types of brain tumors, but most significantly in the case of low-grade gliomas. It was positive in all cases of primary and recurrent low grade gliomas and negative in patients with remission.

FLT exhibited high sensitivity and specificity in case of high grade gliomas. However, it faired suboptimally in case of low grade gliomas – both in case of primary and recurrent tumors. FMISO was sensitive in picking up areas of recurrence, and showed areas of tumor hypoxia. The limited study performed using FET also showed it to be superior to FDG in delineation of tumor extent.

Mild cognitive impairment (MCI) and Dementia:

Of the 117 subjects included with neurocognitive deficits, there were 39 patients with MCI, 40 with Alzheimer's Disease (AD), 14 with Fronto-temporal Dementia (FTD), 13 with Diffuse Lewy Body Dementia (DLBD) and 11 with dementia due to miscellaneous causes. FDG PET/CT was performed in all patients. All patients were followed up clinically for a period of at least one year. MCI patients showed reduced tracer uptake primarily in the mesiotemporal cortex, AD patients in the temporoparietal lobes with advanced cases showing

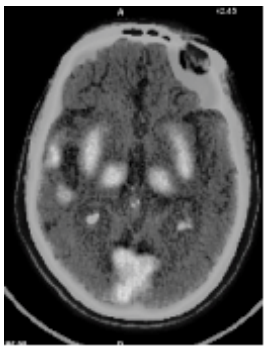

Fig. 3 : An advanced case of Alzheimer's disease : FDG PET/CT scan shows bilateral temporo-parietal and frontal hypometabolism with sparing of occipital cortices.

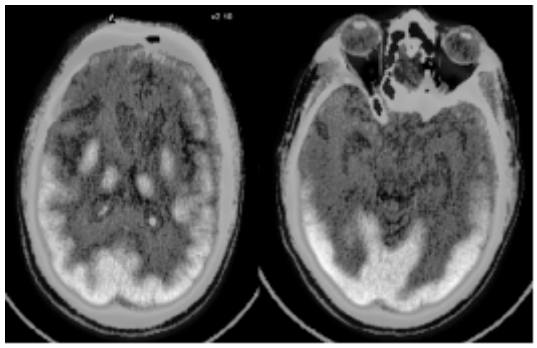

Fig. 4 : A classical case of fronto - temporal dementia : FDG PET/CT scan shows bilateral fronto - temporal hypometabolism.

frontal lobe involvement as well (fig.3), FTD cases in the frontotemporal lobes (fig.4), while DLBD showed global reduction in tracer uptake including the occipital cortices.

Movement disorders:

A total of 104 patients with Parkinsonism were evaluated on FDG PET/CT. Of these, F-DOPA studies were performed on 87 cases. Only patients who could be clinically followed up for at least one year were included in the study. Differentiation of various types of Parkinsonian syndromes was possible on FDG PET/CT studies. Early untreated PD showed pallidothalamic hypermetabolism (fig.5,6). Several patients also showed cortical hypometabolism, predominantly

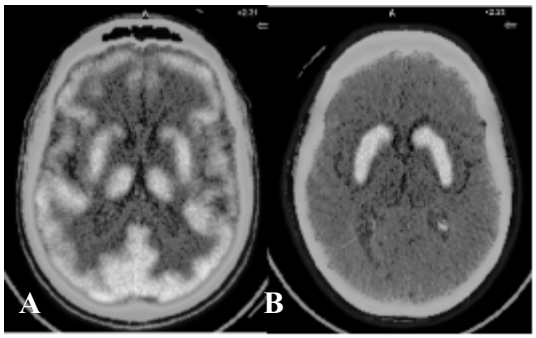

Fig.5 : FDG-PET/CT scan in a normal control (A). Note uniform metabolic activity in cerebral cortices and deep grey matter. The F-DOPA scan (B) in this healthy patient shows intense uptake in the basal ganglia with minimal activity in the cortices.

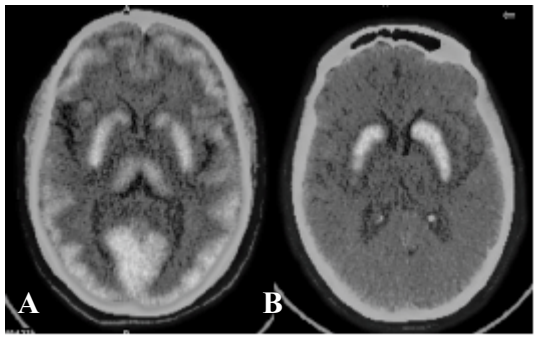

Fig.6 : FDG-PET/CT scan in a patient with Parkinson's disease (A). Note the relative hypermetabolism in the basal ganglia compared to the metabolic activity in cerebral cortices. The F-DOPA scan (B) in this patient shows reduced uptake in bilateral putamen with preserved uptake in the cerebral cortices.

in the parieto-occipital and dorsolateral prefrontal cortices. Patients with progressive supranuclear palsy (PSP) showed hypometabolism predominantly in the mid-brain, basal ganglia and anterior cingulate cortices. Patients with multisystem atrophy (MSA) showed hypometabolism in the pons and dorsolateral putamen, with or without hypometabolism in bilateral cerebellar hemisphere. Patients with corticobasalganglionic degeneration (CBGD) showed asymmetrical hypometabolism in parietal cortices and basal ganglia contralateral to the clinically more affected side. F-DOPA studies showed high sensitivity towards the detection of PD and Parkinsonian syndromes. Reduced uptake in the putamen with relatively normal uptake in the caudate nucleus was seen in cases of PD (fig.5,6). Uniformly reduced F-DOPA uptake was noted in both caudate and putamen in case of Parkinsonian syndromes, although DOPA could not help distinguish between the various categories of Parkinsonian syndromes.

Discussion

PET/CT has been widely used in the study of various central nervous system disorders. A number of different radiopharmaceuticals labelled with positron emitting radioisotopes, such as carbon-11 (^{11}C), fluorine 18(^{18}F) and nitrogen -13 (^{13}N) have been developed for measuring blood flow, neurotransmitter systems and cerebral metabolism (6). The radiopharmaceutical which is most popularly used at present is FDG. Owing to certain inherent limitations of this radiotracer, newer agents are being used to study the pathological states in the brain.

Brain tumors:

The novel PET radiotracers used for oncological applications include tracers for amino-acid synthesis, DNA synthesis, lipid synthesis, hypoxia and angiogenesis. Malignant transformation increases the use of aminoacids for energy, protein synthesis and cell division. Among the radiotracers for protein synthesis, 11C-methionine, 3,4-dihydroxy-6-18F-fluoro-L-phenylalanine (F-DOPA) and O-(2-[18F]fluoroethyl)-l-tyrosine (FET) have been widely studied. These radiotracers have proven superior to FDG in the evaluation of brain tumors as their reduced uptake in healthy brain tissue results in enhanced contrast between the brain tumor and the surrounding normal parenchyma (7). 11C-methionine has proven more efficacious than FDG PET/CT both for the primary detection of tumor and for delineation of its extent. Additionally, it can differentiate tumorous from nontumorous lesions with a high degree of sensitivity and specificity (8). Owing to its selective uptake in brain tumors, 11C methionine PET/CT has also been found to be a useful modality for assessing the size and margins of gliomas that may not enhance on contrast-enhanced Magnetic resonance imaging (MRI) imaging. It also plays an important role as a marker for cell proliferation and angiogenesis (9) and can be used to evaluate tumor grade in

gliomas, thus allowing better tumor prognosis (10). The results of our study corroborate with those of previous studies, with clear evidence of better tumor delineation and improved diagnostic efficacy in both primary and recurrent tumors . Additionally, our study shows that interobserver variability in interpretation is less on 11C-methionine compared to FDG.

Owing to the short half life of 20 minutes that 11C methionine has, its use has been limited to institutions with an on-site cyclotron. Aminoacids labeled with a radiotracer having a longer half-life would be preferred in the routine clinical setting. Of these, F-DOPA and FET have been widely studied. These amino acids are retained in tumor cells, which exhibit higher metabolic activities than most normal cells. Our study shows that F-DOPA has proven superior to FDG in the evaluation of low grade tumors, which are frequently FDG negative. Owing to its affinity for low grade tumors as well, F-DOPA may not be useful for assessing tumor grade. FET PET when combined with MRI significantly improves the identification of cellular glioma tissue (11). In addition, high- and low-grade brain tumors can be differentiated on the basis of the different uptake kinetics of FET. It would be worthwhile to conduct a comparative analysis of these 3 major amino-acid radiotracers, namely 11C methionine, F-DOPA and FET. However, logistical considerations and radiation dose to the patient need to be taken into account, before undertaking such studies.

DNA synthesis is an important prerequisite for cellular proliferation. The most widely used radiotracer for assessing DNA synthesis is 3-deoxy-3-[18F] flurothymidine (FLT). The imaging of cellular proliferation has a potential advantage over glucose imaging because FLT is specific to tumors, while high levels of energy metabolism are also seen with other processes including inflammation(12). Thus, unlike FDG it does not show uptake into inflammatory cells and has been widely used to distinguish benign from malignant pulmonary lesions. Like 11C methionine, the background uptake in normal brain parenchyma is low, thus enhancing tumor detection. It has been found useful for the differentiation of low-grade from high-grade gliomas, but not for distinguishing low-grade gliomas from nonmalignant lesions(13). Our study shows that although FLT performed well in case of high grade gliomas, it faired suboptimally in case of low grade gliomas – both in case of primary and recurrent tumors. Adequate tumor vascularization is an important precondition to tumor growth. Inadequate vascularization would culminate in tumor hypoxia and eventual necrosis. Hypoxic tissue is inherently more resistant to chemotherapy or radiotherapy and this is often responsible for failure of chemo-radiotherapy and an overall poor response. Several *in vivo* PET tracers have been developed to assess tumor hypoxia, e.g.,[18] F fluoromisonidazole (FMISO) and 64/60Cu(II)-diacetylbis (N-4-methylthiosemicarbazone) (64/60Cu-

ATSM), which have a propensity to accumulate in hypoxic rather than normoxic cells. The most extensively used radiotracer for hypoxia is FMISO(14). Inclusion of FMISO imaging data provides information that is complementary to FDG PET data by correlating metabolic activity to tumor hypoxia.

The next generation of PET tracers includes those that will bind to specific cancer-related receptors or antigens (2). These agents would offer tremendous opportunities for selective imaging, thus increasing the sensitivity and specificity for a particular tumor. There would also be enormous potential for directing molecular therapies targeted at these neoplasms. The development of targeted radiolabeled drugs to explore the efficacy of anticancer regimens holds promise for the future.

Dementia

With the introduction of several novel drugs to treat patients with Alzheimer's disease, accurate and early diagnosis is paramount to assess the type of therapeutic intervention. Because the disease is initiated at the molecular and cellular level early in its course, metabolic imaging appears to be the modality of choice for screening patients with memory loss (15). The present study shows that FDG PET/CT is useful in early diagnosis of MCI, which is often a diagnostic dilemma clinically. At the early stages of the disease, functional imaging with flow tracers (using PET or SPECT), or MR perfusion studies may not be sensitive enough to detect evidence of the disease. In advanced cases of course, structural changes would accompany the functional derangements. FDG PET/CT enables the evaluation of glucose metabolism of the brain parenchyma, which is usually done qualitatively or semiquantitatively, although absolute quantification is also possible. In the healthy brain, cerebral blood flow is tightly coupled with local metabolic needs, thus both blood flow and glucose metabolic rate co-vary linearly. Thus, the pattern of distribution of the blood flow tracer oxygen-15-labelled water closely parallels that of the metabolic tracer FDG throughout the cortical surface (15). Dissociations may occur in certain pathological circumstances.

PET/CT studies using FDG in the dementia patient, have enabled early detection and differentiation of the various forms of dementia. Our study, which was the first of its kind performed on the Indian population, showed clear distinction in the patterns of glucose metabolism in the various subtypes, with hypometabolism in the mesiotemporal cortex in MCI, temporoparietal cortex in AD, frontotemporal cortex in FTD and diffuse involvement in DLBD. Further, a significantly higher proportion of frontal lobe involvement was noted in AD in the Indian population. Regional cerebral metabolic changes associated with early AD can be detected with PET/CT even before the symptomatic manifestations of the disease become obvious. FDG PET/CT can also serve explicitly as a

prognostic tool, to determine likelihood of deterioration of mental status in the period following the time of scanning. PET thus has an incremental value beyond conventional clinical assessment.

Movement Disorders

PD is caused by the loss of the pigmented neurons in the substantia nigra and the locus coeruleus. It is believed that initially there is an upregulation of dopamine receptors, followed by a down-regulation that occurs as the disease progresses (16). Conventional imaging techniques such as CT and MRI are not useful for detecting early disease or monitoring subtle changes in disease activity. There have been previous reports of FDG hypermetabolism in the basal ganglia in early PD (17). PD patients have been shown to have mild diffuse cortical hypometabolism compared to controls. In cases of dementia in association with PD, uniform cortical hypometabolism is noted. FDG PET studies enables differentiation of the various Parkinsonian syndromes based on the differential pattern of uptake. In MSA, FDG uptake is reduced in the striatum, frontal cortex and cerebellum (18). As with MSA, FDG PET has identified hypometabolism in striatum, frontal cortex, thalamus and cerebellum in PSP (19). The results of our study, performed on a large scale for the first time on the Indian population, also show differential uptake pattern in the various movement disorders, with pallidothalamic hypermetabolism in PD, hypometabolism predominantly in the mid-brain, basal ganglia and anterior cingulate cortices in PSP, hypometabolism in the pons and dorsolateral putamen in MSA and asymmetrical hypometabolism in parietal cortices and basal ganglia in CBGD.

F-DOPA plays an important role in the diagnosis, evaluation of disease progression and therapeutic monitoring of patients with movement disorders attributed to PD or Parkinsonian syndromes. Patients with PD demonstrate bilaterally reduced FD uptake in the putamen, with normal uptake in the caudate nucleus. Striatal uptake of F-DOPA decreases in proportion to disease severity. Striatal uptake of F-DOPA is markedly reduced both in caudate and putamen in CBGD, PSP and MSA. The findings in our study, which were performed for the first time in the Indian population, corroborated well with that described previously.

Conclusion

PET/CT is a powerful molecular imaging tool in the assessment of neurological disease. The use of FDG and non-FDG novel PET radiopharmaceuticals facilitates the early diagnosis, delineation of extent, prognostication and monitoring of therapeutic response in several neuropathological states, thus strengthening the diagnostic armamentarium of the clinician in his quest to alleviate suffering and conquer disease.

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