Original Article

Comparative study of ^{18}F-DOPA, ^{13}N-Ammonia and F18-FDG PET/CT in primary brain tumors

Mattakarottu J Jacob, Aniruddha G Pandit, Charu Jora, Ravina Mudalsha, Amit Sharma, Harish C Pathak

Departments of Nuclear Medicine and Neurosurgery, Army Hospital, Research and Referral, Delhi Cantt, New Delhi, India

ABSTRACT

Aim: To determine the diagnostic reliability of ^{18}F-FDOPA, ^{13}N-Ammonia and F18-FDG PET/CT in primary brain tumors. We evaluated the amino acid and glucose metabolism of brain tumors by using PET with ^{18}F-FDOPA, ^{13}N-Ammonia and F18-FDG PET/CT. **Materials and Methods**: Nine patients undergoing evaluation for brain tumors were studied. Tracer uptake was quantified by the use of standardized uptake values and the ratio of tumor uptake to normal identical area of contra lateral hemisphere (T/N). In addition, PET uptake with ^{18}F-FDOPA was quantified by use of ratio of tumor uptake to striatum uptake (T/S). The results were correlated with the patient's clinical profile. **Results**: Both high-grade and low-grade tumors were well visualized with ^{18}F-FDOPA. The sensitivity for identifying tumors was substantially higher with ^{18}F-FDOPA PET than with F18-FDG and ^{13}N-Ammonia PET as determined by simple visual inspection. The sensitivity for identifying recurrence in low grade gliomas is higher with ^{13}N-Ammonia than with F18-FDG. **Conclusion**: ^{18}F-FDOPA PET is more reliable than F18-FDG and ^{13}N-Ammonia PET for evaluating brain tumors.

Keywords: ^{13}N-Ammonia, F18-FDG, ^{18}F-FDOPA, brain tumors, diagnosis, PET, sensitivity

INTRODUCTION

CT and MRI are the mainstay of initial evaluation of brain tumors. In post therapy patients, these techniques may not reliably differentiate treatment related scar tissue from viable residual and recurrent tumor tissue, creating a dilemma for the treating clinician. Nuclear medicine techniques which depend on differential metabolism of active tumor from scar tissue will be able to identify viable tumor tissue and will help in treatment. F18-2Fluoro, 2Deoxy d-Glucose (F18-FDG) has been the conventionally used tracer for these metabolic studies. However, because of its diagnostic limitations due to high glucose uptake by normal brain tissue, there is a need for more reliable tracer which can differentiate residual tumor from necrotic tissue. Tracers based on amino acid metabolism have the potential for becoming the ideal tracer in this scenario as multiplying tumor cells utilize amino acids for cell membrane synthesis and mature neurons have minimal uptake of amino acids. We have started a study in brain tumors comparing F18-FDG with two such tracers- ^{13}N- Ammonia and 3,4-dihydroxy-6-F18-fluoro-L-phenylalanine (^{18}F-FDOPA) to substantiate this hypothesis.

Access this article online

Quick Response Code:

Website: www.ijnm.in

DOI: 10.4103/0972-3919.103996

MATERIALS AND METHODS

Nine consecutive preoperative and post-operative cases of brain tumor admitted to our Centre over a period of last two months were included in the study. In treated cases, patients coming after three months of surgery and after six months of completion of radiotherapy were included. The study group comprised of 7 males and 2 females. Of these, two were preoperative cases and remaining were suspected recurrence (n=2 operated for high grade glioma and n=5 for low grade glioma). Out of the 5 known low grade cases, four were histopathology proven astrocytomas and one oligodendroglioma. Both the high grade cases were astrocytomas. Ethical Committee clearance was obtained and informed consent taken from the patients.

^{13}N-Ammonia PET, F18-FDG PET, ^{18}F-FDOPA PET and conventional MR studies (T1WI, T2WI) were obtained in all the patients. PET/CT studies were performed within 2 weeks of MRI studies. PET scanning was performed using Siemens Biograph 2 PET/CT scanner with the patients in the supine position. Patients were fasted for 6-8 hours before F18-FDG PET/CT scanning. A dose of 296-370 MBq of F18-FDG, 555-740 MBq of ^{13}N-Ammonia and 185-296 MBq of ^{18}F-FDOPA was injected intravenously. Images were obtained for a period

Address for correspondence:
Dr. Mattakarottu J Jacob, Department of Nuclear Medicine, Army Hospital Research and Referral, Delhi Cantt, New Delhi-110 010, India.
E-mail: mjjacob12@gmail.com

of 15 minutes, beginning 30 minutes after F18-FDG injection, 5 minutes after ^{13}N-Ammonia injection and 15 minutes after ^{18}F-FDOPA injection. All MR imaging examinations were performed with the clinical 3-T imaging unit (Siemens Trio).

^{18}F-FDOPA uptake in the tumor was visually analyzed as well as quantified using ratios of maximum standardized uptake value (SUV_{MAX}) of tumor with striatum and tumor with corresponding area on the contra lateral side. ^{13}N-Ammonia and F18-FDG uptake were quantified by comparing tumor SUV_{MAX} with corresponding area on the contra lateral side. The results of F18-FDG, ^{13}N-Ammonia and ^{18}F-FDOPA PET/CT were further correlated with patient's clinical profile.

RESULTS

Nine lesions in 9 patients were analyzed. F18-FDG and ^{13}N-Ammonia failed to identify the lesions in both the pre-operative cases. These were picked up by ^{18}F-FDOPA [Figure 1]. Histopathology showed one lesion to be low grade astrocytoma and the other was meningioma [Table 1]. One of the two post-operative symptomatic high grade glioma cases had no abnormal F18-FDG or ^{13}N- Ammonia uptake but ^{18}F-FDOPA showed uptake indicating viable tumor tissue [Figure 2]. The other high grade case was detected by all the three tracers [Figure 3, Table 2]. One of the 5 low grade glioma cases had negative scans with all three tracers. Two of the 5 low grade glioma cases were F18-FDG negative but ^{13}N Ammonia and ^{18}F-FDOPA positive. Rest 2 cases were F18-FDG and ^{13}N-Ammonia negative but ^{18}F-FDOPA positive [Table 3]. In all the above cases, T/S ratio ≥1.0 and T/N ratio ≥1.5 correlated well with patient's clinical profile. Both high-grade and low-grade tumors were well visualized with ^{18}F-FDOPA. In low grade tumor cases, ^{13}N-Ammonia detected more lesions than F18-FDG. The sensitivity for identifying tumors was substantially higher with ^{18}F-FDOPA PET than with F18-FDG PET and ^{13}N-Ammonia while ^{13}N-Ammonia was better thanF18-FDG for recurrence in low grade brain tumors as determined by simple visual inspection.

Table 1: Pre-operative cases

Histopa-thology	Clinical picture	MRI/MRS	F18-FDG	^{13}N Ammonia	F18-FDOPA
Meningioma	Headache, gait ataxia	likely schwannoma Rt CP angle	-ve	-ve	+ve T/S-1.1 T/N-1.5
Low grade astrocytoma	Seizures	s/o low grade glioma RT temporal lobe	-ve	-ve	+ve T/S-1.1 T/N-1.5

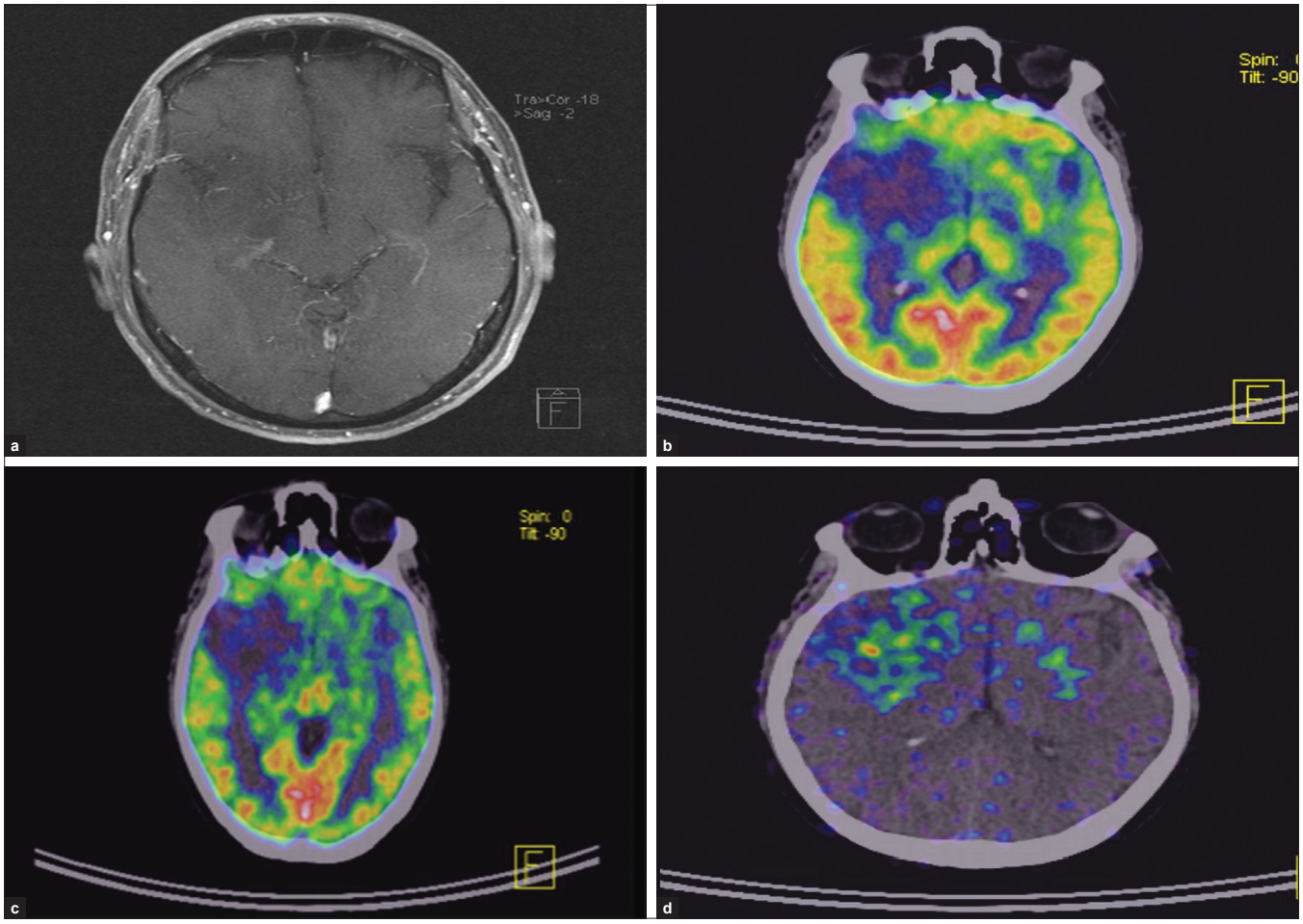

Figure 1: (a) Post contrast MRI shows low grade glioma Rt temporal lobe; (b) No abnormal FDG avid lesion detected in the corresponding region; (c) No abnormal Ammonia avid lesion detected in the corresponding region; (d) F DOPA avid lesion is noted in the RT temporal lobe

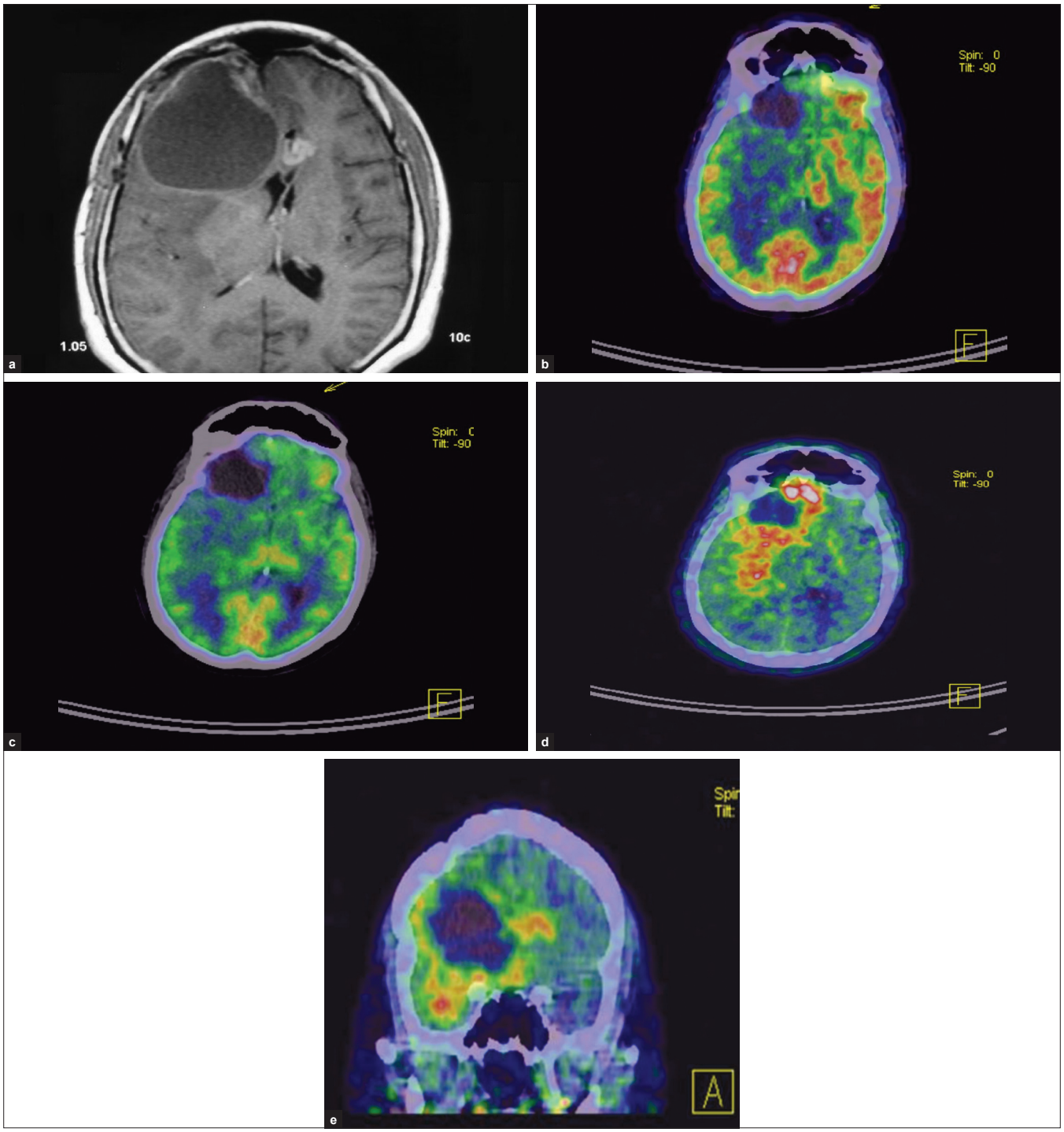

Figure 2: (a) Hypo-intense lesion in RT frontal lobe with mass effect that shows minimal peripheral enhancement. Some of these areas of enhancement are s/o recurrence on MRS; (b) No abnormal FDG avid lesion detected in the corresponding region; (c) No abnormal Ammonia avid lesion detected in the corresponding region; (d) An F-DOPA avid lesion with central hypo-dense hypo-metabolic area in RT frontal lobe causing midline shift of 8mm to left side. The lesion is diffusely extending postero-inferiorly in the parieto-temporal region. Pericallosal spread via genu of corpus callosum to contralateral lobe is seen; (e) F DOPA coronal image shows pericallosal spread via genu of corpus callosum to the Left frontal lobe; typical of butterfly glioma seen in cases of high grade glioma recurrence

DISCUSSION

Treatment of brain tumors consists of a combination of surgery, radiotherapy and chemotherapy. Changes occurring in the treated tissue result in a residual necrotic mass. Distinguishing viable residual or recurrent tumor from such mass or scar tissue is very important. Viable tumor needs further active treatment while scar and necrotic tissue needs only symptomatic treatment. CT and MRI may not differentiate necrotic tissue from viable recurrence/ residual tumor tissue.[1-4] Nuclear medicine techniques which depend on differential metabolism of active tumor from scar tissue will be able to identify residual/ recurrent tumor and will help in treatment.

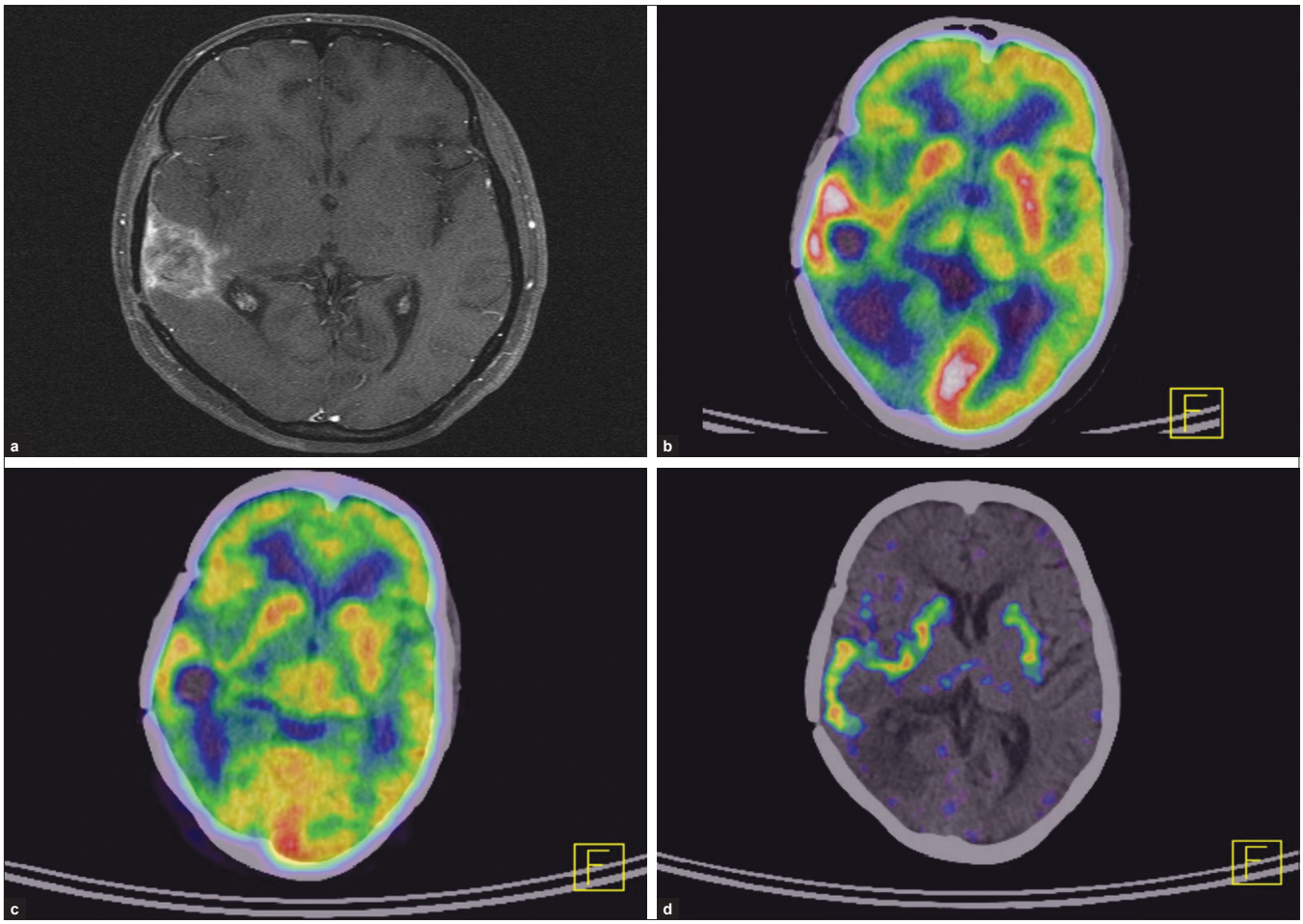

Figure 3: (a) Focal area of bleed with rim enhancement is noted in the post op site in the Rt temporo parietal region; (b) A small FDG avid lesion is noted in the Rt temporo parietal region deep to the craniotomy site; (c) Ammonia avid lesion is noted in the corresponding region; (d) Intense F DOPA uptake is noted in the corresponding region. Physiological F DOPA uptake in Corpus striatum is seen bilaterally

Table 2: Operated low grade cases

Histopathology	Clinical picture	MRI/MRS	F18-FDG	^{13}N Ammonia	^{18}F-FDOPA
Cerebellar astrocytoma	Asymptomatic, follow up visit	Well defined nodular enhancing lesion in post cerebellum	-ve	+ve T/N - 2.42	+ve T/S-0.75. T/N-1.5
RT frontal Astrocytoma	Left sided weakness	-ve	-ve	-ve	-ve
Left frontal astrocytoma	seizure(1 episode), inability to frame certain words	-ve	-ve	+ve	+ve T/S-1.5 and T/N-2.8
Corpus callosum astrocytoma	Headache	Mass lesion at Rt cingulated gyrus extending into adjoining corpus callosum.? residual/edema	-ve	-ve	+ve T/S-1.0 T/N-2.5
Rt frontal oligodendroglioma	Headache	Residual lesion in left frontal lobe- genu of corpus callosum	-ve	-ve	+ve T/S-1.2 T/N-2.3

Table 3: Operated high grade cases

Histopathology	Clinical picture	MRI/MRS	F18-FDG	^{13}N Ammonia	^{18}F-FDOPA
Rt frontal astrocytoma	Seizures, headache, sleep disturbance	Likely recurrence	-ve	-ve	+ve with pericallosal spread to the left frontal lobe T/S-2.4 T/N-3.4
Rt temporo parietal glioblastoma	Headache, gait ataxia	Focal area of bleed at post op site. -ve for recurrence	+ve T/N - 1.27	+ve T/N - 1.29	+ve T/S-1.2 T/N-1.2

Imaging of brain tumors with F18-FDG was the first oncologic application of PET.[5-8] However, recent studies have demonstrated its diagnostic limitations in detection and differentiation of low-grade brain tumors and radiation induced changes.[9]

The uptake of ^{13}N-Ammonia in brain tumors is dependent mainly on two factors, the capillary blood flow in the tumor and the glutamate-glutamine synthetase reaction in the tumor cells which is also the major route for metabolic trapping of ^{13}N-Ammonia in brain tissues.[10]

Amino acid analog PET tracers, like FDOPA, a phenyl alanine analogue, constitute a different class of tumor imaging agents. There is high uptake of these tracers in tumors because tumor cells multiply fast requiring a large pool of amino acids for cell membrane synthesis. FDOPA is neither metabolized nor metabolically trapped, but remains as a part of the large amino acid pool.[11] It is particularly suited for imaging of brain tumors because of the low uptake in normal brain tissue, other than corpus striatum neurons. This results in a high target to background ratio. In corpus striatum, the neurons metabolize FDOPA to 6 Fluoro Dopamine, and hence may demonstrate higher FDOPA uptake than tumor tissue.[11]

Preoperative cases were included to document efficacy of the three tracers for brain tumor imaging followed by histopathological validation and also to identify site of highest metabolic activity for selecting site for biopsy. In both the pre op cases, only ^{18}F-FDOPA was able to identify the lesions [Figures 1]. In post-operative cases also, ^{18}F-FDOPA identified lesions in more cases and delineated the lesions better. Our findings match those of Chen, *et al*.[9] In both the operated high grade tumor cases, it was found to be better than MRI and MRS at lesion detection and clinical correlation [Figure 2 and 3]. In Figure 2a and d, though MRI is suggestive of recurrence, the diffuse involvement of adjacent parieto temporal lobe and peri callosal spread to the contra lateral side (butterfly glioma) [Figure 2e] were missed on MRI. Findings of ^{18}F-FDOPA studies correlated better with the clinical picture in this case. In all symptomatic cases, ^{18}F-FDOPA was positive with T/S ratio ≥1 and T/N ratio ≥1.5 that has been taken as the reference cut off in some studies.[9,11-12] N-Ammonia was found to be better than F18-FDG at identifying recurrence in low grade tumors. Comparative efficacy of F18-FDG and ^{13}N-Ammonia in our study matches with the results of Zhang Xiangsong Æ Chen Weian.[10] Comparison of ^{13}N-Ammonia and ^{18}F-FDOPA reveals ^{18}F-FDOPA to be a superior tracer for detection of recurrence. Literature search reveals this to be the first study comparing these three tracers. The number of cases is presently small to draw statistical conclusions; however, it suggests superiority of ^{18}F-FDOPA for detection of residual and recurrent brain tumor. The data needs to be validated further with a larger study inducting more number of patients.

CONCLUSION

^{18}F-FDOPA PET/CT picks up more lesions and shows more intense uptake in all the suspected lesions compared to ^{13}N-Ammonia and F18-FDG, thus making it a better tracer for detection of residual or recurrent brain tumor and differentiating it from treatment related scar tissue. Even though ^{13}N-Ammonia is better than F18-FDG, compared to ^{18}F-FDOPA, it also can miss actual cases of tumor recurrence. ^{18}F-FDOPA PET/CT scan findings match with clinical profile and histopathological findings. Thus, in cases of clinically probable brain tumor recurrence, ^{18}F-FDOPA PET/CT will be of great help for the correct management of the case.

ACKNOWLEDGEMENT

Radiochemists, Mr. Dhananjay K Singh, Mr. Rajeev Kumar and Technician Mr. Abhay Kumar.

REFERENCES

1. Dooms GC, Hecht S, Brant-Zawadzki M, Berthiaume Y, Norman D, Newton TH. Brain radiation lesions: MR imaging. Radiology 1986;15:149-55.
2. Van Dellen JR, Danziger A. Failure of CT to differentiate between radiation necrosis and cerebral tumor. S Afr Med J 1978;53:171-2.
3. Nelson DR, Yuh WT, Wen BC, Ryals TJ, Cornell SH. Cerebral necrosis simulating an intraparenchymal tumor. AJNR Am J Neuroradiol 1990;11:211-2.
4. Nelson SJ, Huhn S, Vigneron DB. Volume MRI and MRSI techniques for the quantitation of treatment response in brain tumors: presentation of a detailed case study. J Magn Reson Imaging 1997;7:1146-52.
5. Patronas NJ, Di Chiro G, Brooks RA, DeLaPaz RL, Kornblith PL, Smith BH, *et al*. Work in progress: F18 fluorodeoxyglucose and positron emission tomography in the evaluation of radiation necrosis of the brain. Radiology 1982;144:885-9.
6. Di Chiro G, Oldfield E, Wright DC, De Michele D, Katz DA, Patronas NJ, *et al*. Cerebral necrosis after radiotherapy and/or intraarterial chemotherapy for brain tumors: PET and neuropathologic studies. AJR Am J Radiol 1988;150:189-97.
7. Doyle WK, Budinger TF, Valk PE, Levin VA, Gutin PH. Differentiation of cerebral radiation necrosis from tumor recurrence by F18-FDG and ^{82}Rb positron emission tomography. J Comput Assist Tomogr 1987;11:563-70.
8. Wong TZ, van der Westhuizen GJ, Coleman RE. Positron emission tomography imaging of brain tumors. Neuroimaging Clin N Am 2002;12:615-26.
9. Chen W, Silverman DH, Delaloye S, Czernin J, Kamdar N, Pope W, *et al*. ^{18}F-FDOPA PET imaging of brain tumors: Comparison study with F18-FDG PET and evaluation of diagnostic accuracy. J Nucl Med 2006;47:904-11.
10. Xiangsong Z, Weian C. Differentiation of recurrent astrocytoma from radiation necrosis: A pilot study with ^{13}N-NH3 PET. J Neurooncol 2007;82:305-11.
11. Schiepers C, Chen W, Cloughesy T, Dahlbom M, Huang SC. ^{18}F-FDOPA kinetics in brain tumors. J Nucl Med 2007;48:1651-61.
12. Fueger BJ, Czernin J, Cloughesy T, Silverman DH, Geist CL, Walter MA, *et al*. Correlation of 6-F18-Fluoro-L-Dopa PET uptake with proliferation and tumor grade in newly diagnosed and recurrent Gliomas. J Nucl Med 2010;51:1532-8.

How to cite this article: Jacob MJ, Pandit AG, Jora C, Mudalsha R, Sharma A, Pathak HC. Comparative study of ^{18}F-DOPA, ^{13}N-Ammonia and F18-FDG PET/CT in primary brain tumors. Indian J Nucl Med 2011;26:139-43.

Source of Support: Nil. **Conflict of Interest:** None declared.