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Clinical utility of 18F-FDG-PET/MRI brain in dementia: Preliminary experience from a geriatric clinic in South India

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ABSTRACT

Background: ^{18}F-FDG-PET is a potential sensitive biomarker indicating neuronal damage. ^{18}F-FDG-PET has proven to be useful in subtyping dementia. Utility of simultaneous ^{18}F-FDG-PET and MRI-brain was investigated in the evaluation of dementia in this facility.
Method: All case notes of patients who underwent 18 F-FDG-PET/MRI brain attending the Geriatric Clinic for 18 month period between January 2017 and June 2018 were retrospectively reviewed. Their socio-demographic details, MRI-brain finding, ^{18}F- FDG-PET findings and comorbid illnesses were studied.
Results: A total of 21 patients underwent ^{18}F-FDG-PET/MRI brain during study period. The mean age was 61.23, SD-8.6 years (range: 36–75 years). Among them 5 (23.8%) had Mild Cognitive Impairment (MCI) and 16 (76.2%) had dementia. Majority of patients had early onset cognitive decline (76.2%). Based on the pattern of hypometabolism, the MCI group had one patient each indicative of AD, Semantic-Frontotemporal dementia (Semantic-FTD), mixed Alzheimer's dementia (AD + FTD) and two patients had patterns suggestive of Behaviour Variant of FTD (Bv-FTD). In Dementia group the pattern of hypometabolism was indicative of Bv-FTD in seven, AD in four, Posterior Cortical Atrophy (PCA) in one, Semantic-FTD in one, Mixed AD-Diffuse Lewy Body Dementia (DLBD) in one and no specific pattern in two patients. MRI and 18 F-FDG-PET brain had concordance in 9 (56.26%) patients.
Discussion: ^{18}F-FDG-PET/MRI helped in overall clinical diagnosis and management in 19 (90.5%) patients especially with early onset dementia. In MCI group it indicated underlying aetiology and in dementia group it helped in subtyping.
Conclusion: The study supports the role of ^{18}F-FDG-PET/MRI as an emerging diagnostic tool to assist in dementia evaluation in India.

1. Introduction

Dementia is a disease of the brain with cardinal features of progressive decline in memory and intelligence, with functional impairment and later becomes dependant for activities of daily living. Most of persons with dementia presenting in late life are degenerative and have irreversible course (Burns and Iliffe, 2009). An elderly presenting with cognitive impairment or behavioural problems requires a systematic evaluation including detailed history, objective assessments and appropriate investigations. An earlier and accurate diagnosis of dementia is very important to clinicians, patients and their families. In case of clinicians it helps in prognostication of the case, rationalising medication and avoiding certain medication. For patients and family members it helps in planning their future actions, adjusting to the new scenario, planning for home based and palliative care in terminal stage (Burns, 2012; Robinson et al., 2015). The reported sensitivity and specificity (range) of clinical diagnostic criteria for Alzheimer's dementia (AD) ranges from 53.0%–100% and 55%–99% respectively (Gaugler et al., 2013; Knopman et al., 2001). The clinical diagnostic criteria for fronto-temporal dementia (FTD) and lewy body dementia (DLBD) has good specificity but have poor sensitivity (Luis et al., 1999; Mendez et al., 2007). There is a need to increase the diagnostic sensitivity and specificity for dementia/neurodegenerative illnesses.

The diagnosis of dementia is moving from a primarily clinical

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diagnosis to more objective biomarker based diagnosis with more understanding (Ahmed et al., 2014). Recent advances in dementia evaluation as per National Institute of Aging (NIA) and Alzheimer's Association (AA), identified specific biomarkers to improve the accuracy of diagnosis (Jack et al., 2018). These biomarkers are broadly classified as structural imaging, molecular imaging and CSF biomarkers (Bayer, 2018). Structural imaging such as either CT-brain or MRI-brain are recommended in dementia evaluation. Structural imaging primarily helps in ruling out reversible aetiologies such as tumours, infarcts and signs of neuroinfection (Health Quality Ontario, 2014; Pasi et al., 2011). In sub-set of cases the particular pattern of cortical atrophy and subcortical features guides in confirming the phenotype (Harper et al., 2014). Molecular imaging such as amyloid PET and CSF amyloid-beta 42 and tau ratio are the recommended biomarkers in dementia evaluation (O'Brien and Herholz, 2015; Simonsen et al., 2017). These investigations though they are highly sensitive and specific for diagnosing AD and differentiating AD from other dementia subtypes there are logistic difficulties in India. One is the cost, another is standardisation problems and most importantly unavailability. In this scenario other relatively less costlier and emerging investigational tools such as 18 F-FDG-PET need to be studied in dementia evaluation.

18 Flouro de oxy glucose – Positron Emission Tomography (^{18}F-FDG- PET) is a type of the molecular imaging with its increasing utility in the last decade in dementia evaluation (Portnow et al., 2013). ^{18}F-FDG-PET brain is based on astrocyte/neuronal glucose consumption and in turn metabolic activity (Basu et al., 2014). Decrease of ^{18}F-FDG PET uptake is considered to be a direct indicator of synaptic dysfunction. ^{18}F-FDG-PET is known to detect the hypometabolism before structural changes become evident. It helps in detecting the underlying pathology in cases with subtle or mild cognitive decline (Pagani et al., 2017; Tripathi et al., 2013). ^{18}F- FDG-PET has shown to improve accuracy of dementia diagnosis and also sub-typing of dementia (Foster et al., 2007; Morbelli et al., 2015; Shivamurthy et al., 2015). In resource limited country like India, investigative modalities like 18 F-FDG-PET became available only in the last decade. ^{18} F-FDG-PET has a potential role in the diagnostic evaluation of those cases with diagnostic uncertainity in the clinical evaluation. A prior study from northern India reported on potential usefulness of ^{18}F-FDG-PET/MRI brain in evaluation of neurodegenerative conditions (Jena et al., 2015). There are very few studies on dementia in Indian set up, and therefore the objective was to examine utility of simultaneous ^{18}F-FDG-PET/MRI brain as an investigational tool in diagnosis and subtyping of dementia in our facility.

2. Material and methodology

The current study was conducted in National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru. The design adopted for the study was retrospective. Ethical approval was obtained from Institutional Ethics Review Board. The sample for the study were patients seeking treatment from Geriatric Clinic and Services, NIMHANS with diagnosis of dementia or Mild Neurocognitive disorder as per the DSM-5 diagnostic criteria from January 2017 to June 2018. The medical records of all those patients who underwent ^{18}F-FDG-PET/MRI brain specifically were traced and reviewed. Details regarding their socio-demographic, clinical features, indication for ^{18}F-FDG-PET, differential diagnosis, comorbid psychiatric and medical illness was reviewed. Imaging details were obtained from hospital electronic imaging data base which provides brain images of every patient with documented findings. The reported finding in the MRI- brain and ^{18}F- FDG-PET were based on consensus from the experts specialized in Neuro-Radiology and Nuclear Medicine. Confidentiality regarding the identity of these patients was ensured. However, the brain imaging experts were not blind for the clinical diagnosis as the clinical details of the patient is generally available to them for clinical reporting of brain scans as per the protocol followed in our institute.

3. 18F FDG-PET MRI (hybrid machine) procedure

All the patient who were referred for ^{18}F FDG-PET/MRI had to be nil oral 4–6 hours prior to imaging. On the day of the scan they were assessed for presence of any ferromagnetic implants in the body. Fasting blood sugar was measured in all the patients prior to tracer injection. ^{18}F-FDG tracer was administered intravenously and the dose was calculated depending of body weight. Post injection all the patients were placed in a dim lit room, with a calm environment and specific instruction for the patients to keep their eyes open during the entire uptake phase was followed. All the patients underwent Brain PET MRI in Siemens Biograph Simultaneous PET/ MRI scanner (Erlangen, Germany) after approximately 45 min ± 15 min post ^{18}F-FDG injection. Whole brain images PET images with appropriate attenuation sequence was acquired for 10 min along with mutiplanar and multisequence MR in 3-D mode using a simultaneous Siemens mMR Biograph scanner. Reconstruction of the acquired data was performed so as to obtain fused PET-MR images in trans-axial, coronal and sagittal views. These images were then sent to hospital electronic imaging data base and are accessible to specialist doctors in the hospital. 18 F-FDG-PET/MRI is expensive (ranges from 6000 rupees to 16,000 rupees depending on the income status of the patients) compared to the PET CT. The infrastructure cost required for PET MRI Centre (approximately 83–100 Cr) is expensive compared to PET CT facility. Since this was a retrospective analysis, the patients were required to pay for the scans.

4. Visual interpretation

All the images acquired were viewed independently by Nuclear Medicine Physician and Neuro Radiologist. The images of the PET were viewed on the SYNO Via workstation. The images were initially analysed visually. Post visual analysis the images were loaded on the SCENIUM software provided by SIEMENS to obtain a quantitative results of the visually analysed data of the patients. Database Comparison is a software solution to compare a brain PET scan of a patient to a database of brain images of the same radiotracer composed of scans from confirmed normal individuals. The main purpose of the Database Comparison workflow was to calculate and display voxel-wise comparison statistics, highlighting areas of the subject dataset where tracer uptake is different from that in the normal population used to build the selected database. Though this SCENIUM software is not validated for MR attenuation correction, in our study population it was found to benefit and add on to the visual interpretation of the scans obtained.

5. Results

Out of 237 new patients with MCI and dementia seen in our clinic during the study period (2017–2018), 21 patients had diagnostic issues in terms of subtyping and finding the underlying etiology in case of MCI. Majority of these patients have young onset (76.2%) with atypical clinical presentation. These 21 patients underwent 18 F-FDG PET/MRI-brain in our facility. The mean age of these patients was 61.3 (SD- 8.6) years (median-62.0 & range: 36–75 years). 18 (85.7%) were men and 3 (14.2%) were women. 16 (76.2%) patients presented with early onset cognitive decline (< 65 years) and 5 (23.8%) presented with late onset cognitive decline (> 65 years). Among them 5 (23.8%) patients presented with mild cognitive decline and were clinically diagnosed as mild cognitive impairment (MCI) as per National institute of Aging and Alzheimer's Association criteria (NIA-AA). Majority of patients (16, 76.2%) presented with significant cognitive decline interfering with activities of daily living and were diagnosed with dementia. (Table 1)

There were two major reasons for choosing ^{18}F-FDG-PET/MRI-brain studies in these patients; for evaluation of mild cognitive impairment (MCI) in 5 patients and for subtyping the dementia (phenotype) in 16 patients with clinically confirmed dementia.

The mean age of patients in MCI group and Dementia group were

Table 1
Socio-demographic and clinical features.

S.No	Domain	Results
1.	Total sample	N = 21
2	Age (Mean)	61.3 (SD-8.6) years
3	Men	18 (85.7%)
4.	Women	3 (14.2%)
5	Mild cognitive impairment (MCI) group	5 (23.8%)
6	Dementia group	16 (76.2%)
7	Early onset dementia (< 65 years)	14 (87.5%)
8	Late onset dementia (> 65 years)	2 (12.5%)
9	HMSE of MCI group (Mean)	28 (SD-2.45)
10	HMSE of Dementia group (Mean)	17.14 (SD- 8.1)

HMSE: Hindi Mental Status Examination.

68.4 (SD-4.93) years and 59.06 (SD-8.42) years respectively. The duration of illness in these three groups were 2.9 (SD-1.7) years and 1.92 (SD-1.02) years respectively. Comorbid psychiatric illness was present in two patients in MCI group and three in dementia group. The psychiatry illness in the subjects were anxiety disorder and bipolar illness in MCI group. Three patients in dementia group had psychosis, depressive disorder and Benzodiazepine dependence respectively. The comorbid psychiatry conditions were evaluated and treated adequately. The psychiatric illness also lead to difficulty in subtyping dementia. The clinical diagnosis of these patients and MRI-brain finding were as shown in Table 2.

Based on the pattern of hypometabolism, the MCI group had one patient each indicative of AD, Semantic-FTD, mixed AD + FTD and two patients had patterns suggestive of Behaviour Variant of FTD (Bv-FTD). In Dementia group the pattern of hypometabolism was indicative of Bv-FTD in seven, AD in four, Semantic-FTD in one, PCA variant in one, Mixed pattern (AD + DLBD) in one and no specific pattern in 2 patients (Table 3). MRI and ^{18}F-FDG-PET brain had similar finding with atrophy and hypometabolism involving the same regions in nine (42.8%) patients. ^{18}F-FDG-PET has not shown any specific pattern in two (9.5%) patients (did not suggest any clear subtype) (Table 3). ^{18}F-FDG-PET images of AD and Bv-FTD of two patients from our sampleare shown in Figs. 1 and 2.

Table 3
18F-FDG PET pattern in the sample.

18F-FDG PET pattern suggests	MCI	Dementia
AD	1	4
PCA variant of AD	–	1
Bv-FTD	2	7
Semantic-FTD	1	1
Mixed pattern	1 (AD + FTD)	1 (AD + DLBD)
No specific pattern	0	2

MCI- Mild cognitive impairment, AD- Alzheimer's dementia, Bv-FTD-Behavioural Variant of Fronto-temporal dementia, DLBD- Diffuse Lewy body dementia. PCA-Posterior Cortical Atrophy

6. Discussion

^{18}F-FDG-PET was not routinely done as part of cognitive evaluation in our Clinic. Of the 237 patients with probable dementia seen in the Geriatric Clinic, NIMHANS only 21 patients underwent ^{18}F-FDG-PET/MRI. Many of these had been referred for diagnostic confirmation. In case of MCI patients, 5 underwent ^{18}F-FDG-PET/MRI, the reason being to find early aetiological diagnosis. Another reason for advising ^{18}F-FDG-PET/MRI in MCI patients was to prognosticate risk for progression to dementia in these patients. Recently proposed NIA-AA, research frame work criteria advocated for the use of biomarkers to increase the diagnostic accuracy. ^{18}FDG-PET is included as one of the tau-mediated neuronal injury marker for AD and MCI (Jack et al., 2018). In the 2014 revised International Working Group (IWG) criteria for AD, ^{18}F-FDG-PET is not included as the diagnostic marker but for monitoring the course of disease (Dubois et al., 2014). A Pooled meta-analysis of 27 studies evaluating 18 F-FDG-PET in the diagnosis of AD found 90% sensitivity (95% confidence interval (CI), 84–94%) and 89% specificity (95% CI, 81–94%) compared to non-demented controls (Bloudek et al., 2011). In case of MCI, ^{18}F-FDG-PET pooled estimates exhibited 88.8% sensitivity (95% (CI), 82.2–93.6%) and 84.9% specificity (95% CI, 78.1–90.3%). Whereas structural MRI exhibited 72.8% sensitivity (95% CI, 65.1–79.6%) and 81% specificity (95% CI, 65.1–79.6%) (Yuan et al., 2009). This proves that during MCI and early stages of AD, ^{18}F-FDG-PET is better diagnostic tool than structural MRI. The reason could be the minimal gray matter atrophy in these early stages is difficult to pick

Table 2
Clinical diagnosis and structural imaging finding in the sample.

Clinical diagnosis		MRI-brain features
Mild cognitive Impairment group	–	Diffuse mild cerebral atrophy (2 patients), Asymmetric atrophy (left > right) with left medial and lateral temporal atrophy including left perisylvian (1 patient), Bilateral parietal atrophy (1 patient), Prominent flow void across aqueduct with high parietal sulci effacement suggestive of NPH (1 patient), White matter hyperintensities (3 patients in combination with above),
Dementia group	AD Phenotype	Bilateral diffuse symmetric atrophic changes (5 patients), Dilated sylvain fissures with parietal sulci effacement and increased flow void across aqueduct noted suggestive of NPH (1 patient), Mild atrophy in the bilateral frontal and parietal lobes and mild asymmetrical atrophy in the temporal and parietal lobes (3 patients), Moderate to marked cerebral atrophy, predominantly in the B/L fronto-temporal and parietal regions (left > right) with atrophied B/L medial temporal lobes (2 patients), White matter hyperintensities noted in the deep white matter confluent in nature (4 patients in combination with above)
	Bv-FTD Phenotype	Atrophic pattern is bilateral- frontal > medial & lateral temporal > parietal lobe atrophy (1 patient) Dilatation of ventricles disproportionate to the atrophy and effaced parietal sulci suggestive of NPH (1 patient). White matter hyperintensities to suggest small vessel disease (1 patient in combination with above)
	Language variant-FTD Phenotype	Diffuse cerebral cortical atrophy- asymmetric pattern (left > right) parietal > perisylvian > medial temporal > frontal lobe (1 patient)
	DLBD phenotype	Diffuse cerebral cortical atrophy is noted with bilateral parietal > frontal > medial temporal (1 patient) Atrophy of bilateral temporal lobes, hippocampus, and parietal regions (1 patient) Bilateral cerebral white matter small vessel ischemic changes (2 patients in combination with above)

MCI- Mild cognitive impairment, AD- Alzheimer's dementia, Bv-FTD-Behavioural Variant of Fronto-temporal dementia, DLBD- Diffuse Lewybody dementia, NPH-Normal pressure hydrocephalus.

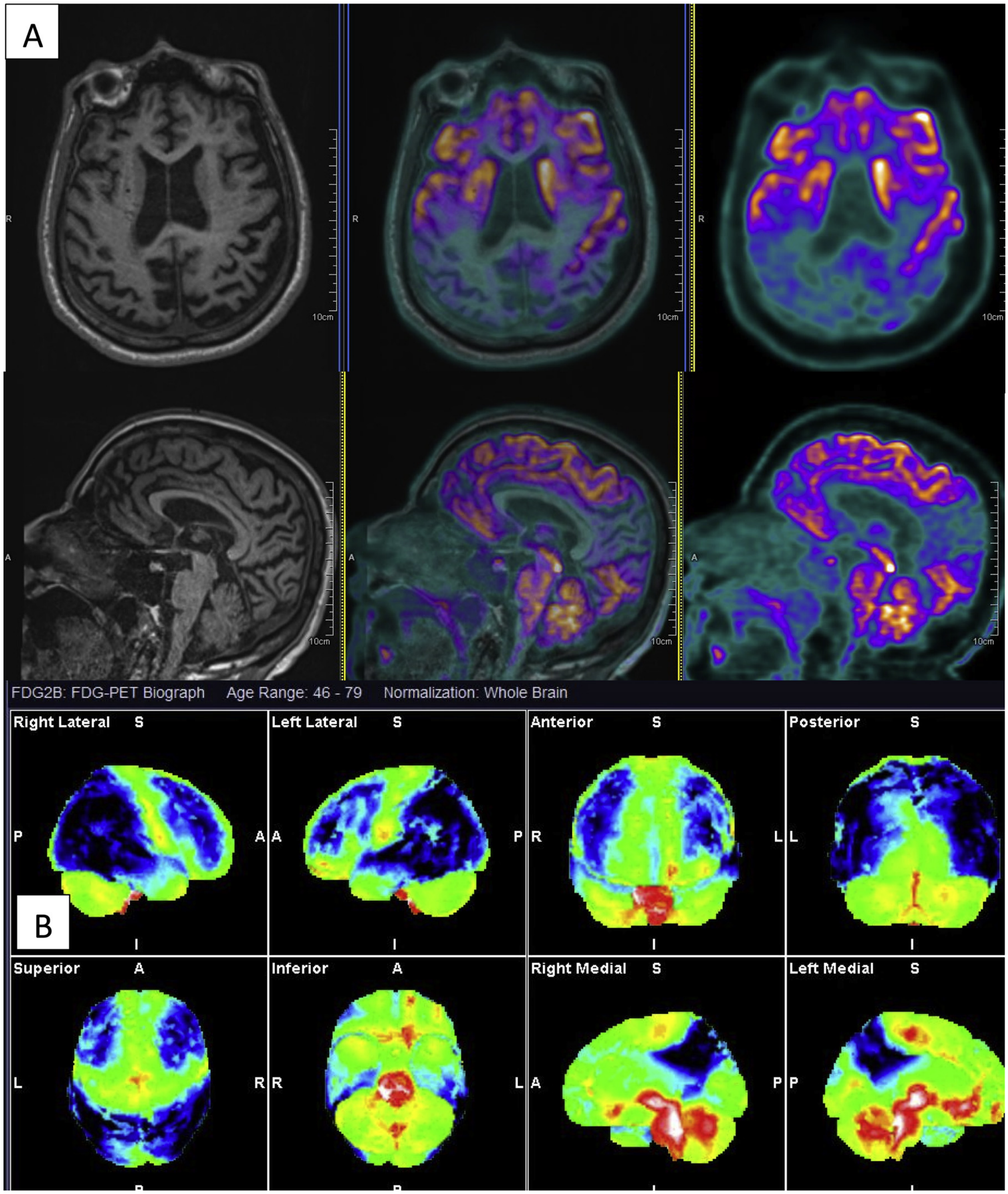

Fig. 1. (A) MR, Fused PET MR and PET images in axial and sagittal sections show severe decrease in tracer uptake in bilateral posterior parietal lobes involving the precuneus, bilateral frontal lobes and temporal lobes suggestive of AD. (B): Quantitative analysis of the images show similar findings as described above.

on structural MRI, whereas ^{18}F-FDG-PET which actually indicates the synaptic dysfunction is more sensitive.

Another indication for doing ^{18}F-FDG-PET/MRI in our patients was subtyping dementia. 16 patients with dementia diagnosis underwent ^{18}F-FDG-PET only for confirmation of phenotype (sub-type of dementia). The commonest reason is to differentiate between AD and FTD in our sample and in two patients to differentiate AD and DLBD. Studies have reported that ^{18}F-FDG-PET is useful in differentiating AD from FTD and also DLBD (Chertkow and Nikelski, 2011; Festari et al., 2017; Foster et al., 2007). The pattern on ^{18}F-FDG-PET indicative of AD is hypometabolism in bilateral temporo-parietal region, precuneus and posterior cingulate cortex (Silverman et al., 2001; Tripathi et al., 2013). In FTD the common pattern is bilateral prefrontal cortex, lateral temporal lobes and anterior cingulate cortex (Foster et al., 2007; Jeong et al., 2005). Whereas in DLBD it is the primary visual cortex and occipital association area hypometabolism (Albin et al., 1996; Minoshima et al., 2001). There will be subtle differences depending on the subtypes in each diagnostic category and on stage of dementing illness. However in two patients in our sample with diagnosis of possible DLBD and mixed dementia (traumatic brain injury + AD) respectively, no specific pattern was found on the ^{18}F-FDG-PET. In these two patients the hypometabolism on ^{18}F-FDG-PET did not corroborate with clinical diagnosis or any other common dementia syndromes.

^{18}F-FDG-PET also helped in subtyping our patients who had higher comorbid psychiatric illness preceding the cognitive decline. There are studies on ^{18}F-FDG-PET in few psychiatric conditions which helps in

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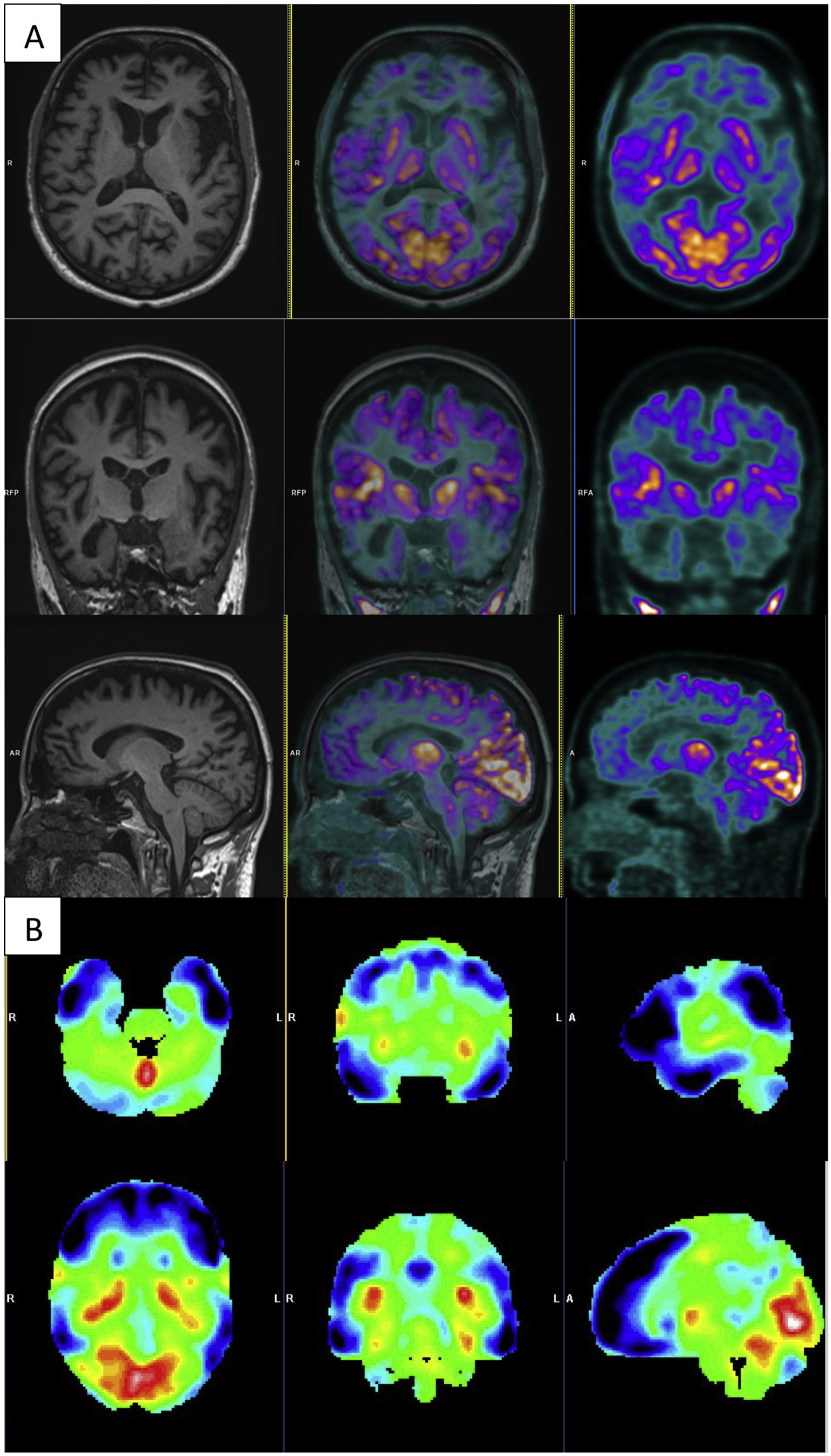

Fig. 2. (A) Axial, Coronal and Sagittal images MRI, Fused PET MRI showing decrease trace uptake in bilateral frontotemporal and anterior cingulate cortex suggestive of Bv-FTD (B) Quantitative analysis of the images show similar findings as described above.

differentiating each other and from various sub-types of dementia. Resting state $^{18}F^{-}$FDG-PET studies in bipolar individuals have shown hypermetabolism in anterior limbic region (anterior temporal cortex, amygdala, parahippocampal region) and hypometabolism in prefrontal cortex (dorsolateral prefrontal cortex and anterior cingulate cortex) which is found to become normal after remission (Brooks et al., 2009; Kupferschmidt and Zakzanis, 2011). Patients with depressive disorder showed hypometabolism on ^{18}F-FDG-PET in Cingulate Gyrus, Superior Frontal Gyrus, Rectal Gyrus and Orbital Gyrus compared with the healthy control group (Wei et al., 2016). Contrary to the above, patients with schizophrenia were known to have hypermetabolism on ^{18}F-FDG-PET in the medial temporal regions, basal ganglia and left thalamic regions correlating with positive symptoms (delusion and hallucination). Schizophrenia patients also found to have cerebellar hypometabolism correlating with cognitive dysfunction (Seethalakshmi et al., 2006). In our sample five patients with bipolar disorder, depression, anxiety disorder and benzodiazepine dependence as comorbid psychiatric condition were finally subtyped as Bv-FTD following ^{18}F-FDG PET. Similarly one patient with late onset psychosis finally diagnosed as mixed etiology AD with DLBD features following ^{18}F-FDG-PET.

To summarise, ^{18}F-FDG-PET/MRI helped in MCI dementia evaluation. ^{18}F-FDG-PET/MRI was also helpful in subtyping the dementia. It has concordance with differential clinical diagnosis in nineteen patients (90.5%) that were considered prior to scan and has helped in overall management. However in two (9.5%) patients, ^{18}F-FDG-PET/MRI did not show any specific pattern. The advantages of ^{18}F-FDG-PET/MRI are it's relatively simple procedure, being non-invasive with very few contraindications and can be done even in outpatient basis. It has relatively less radiation exposure compared to Computed tomography (CT). It has advantage of detecting the pathological /metabolic changes before the appearance of clinical symptoms. This is particularly relevant in early stages of dementia. Another advantage of hybrid machine (used in our facility) was both MRI-brain and ^{18}F-FDG-PET can be done simultaneously. In cognitively impaired elderly individuals due to their behavioural problems may require sedation for any imaging procedure. In this facility ^{18}F-FDG-PET/MRI under sedation was done in a small proportion of patients which gave structural and fuctional information at one procedure. It has prevented requirement of anaesthesia multiple times for CT, MRI, and ^{18}F-FDG-PET if we had done separately each.

Few drawbacks of ^{18}F-FDG-PET are exposure to radiation, limited spatial resolution as compared to MRI and cost effectiveness. Though advantages outnumber the disadvantages, ^{18}F-FDG-PET/MRI in our country is an emerging diagnostic tool. However, it should be indicated only after thorough clinical and cognitive evaluation in a subset of patients if there are diagnostic issues.

7. Strengths

To the best knowledge, authors believe this is the first study from south India using ^{18}F-FDG-PET/MRI-brain in dementia evaluation. Another strength of the study was clinical assessment and Imaging was reported by the qualified experts in the field.

8. Limitation

There are few limitations in this study. The retrospective study design which has inherent limitation in concluding the usefulness of ^{18}F-FDG-PET/MRI. Our study included a smaller sample. Another limitation is sampling bias as it involved clinic based sample. There was no blinding to the MRI and ^{18}F-FDG-PET reading as two experts will have access to both images and finding were based on consensus among them. This was because it was done for clinical purpose rather than for a study.

9. Conclusion

The available diagnostic criteria has poor sensitivity and it needs to be augmented by development of biomarkers to increase diagnostic accuracy. Amyloid PET imaging and CSF biomarkers which are recommended for subtyping are generally unavailable to clinicians in India or invasive. In this scenario ^{18}F-FDG-PET/MRI which is a neuronal injury biomarker can be used as a non-invasive emerging tool to help in dementia diagnosis and subtyping in India. In the limited sample of our patients, ^{18}F-FDG-PET/MRI-brain certainly helped in subtyping and prognosticating MCI. Though it is early to recommend ^{18}F-FDG-PET/MRI brain as part of routine dementia evaluation, it is can be used judiciously in few cases with early onset and diagnostic complexity.

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Declaration of Competing Interest

None.

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