ORIGINAL ARTICLE

^{18}F-FDG PET/CT for the pre-surgical localization of epileptogenic focus among paediatric patients with drug resistant epilepsy in Malaysia: perspective of a nuclear medicine physician

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ABSTRACT

Background: Scalp video electroencephalography monitoring (VEM) and brain MRI sometime fail to identify the epileptogenic focus (EF) in patients with drug resistant epilepsy (DRE). ^{18}F-FDG PET/CT has been shown to improve the detection of EF in patients but is not widely used in Malaysia. Thus, the objective of this study was to identify whether ^{18}F-FDG PET/CT conferred an added benefit in the pre-surgical evaluation of DRE.

Methods: Retrospective review of 119 consecutive paediatric patients referred for ^{18}F-FDG-PET/CT at the Department of Nuclear Medicine of the National Cancer Institute, Putrajaya. All had DRE and underwent evaluation at the Paediatric Institute, Hospital Kuala Lumpur. Visually detected areas of ^{18}F-FDG-PET/CT hypometabolism were correlated with clinical, MRI and VEM findings.

Results: Hypometabolism was detected in 102/119 (86%) ^{18}F-FDG-PET/CT scans. The pattern of hypometabolism in 73 patients with normal MRI was focal unilobar in 16/73 (22%), multilobar unilateral in 8/73 (11%), bilateral in 27/73 (37%) and global in 5/73 (7%) of patients; whilst 17/73 (23%) showed normal metabolism. In 46 patients with lesions on MRI, ^{18}F-FDG-PET/CT showed concordant localisation and lateralization of the EF in 30/46 (65%) patients, and bilateral or widespread hypometabolism in the rest. Addition of ^{18}F-FDG PET/CT impacted decision making in 66/119 (55%) of patients; 24/73 with non-lesional and 30/46 patients with lesional epilepsies were recommended for surgery or further surgical work up, whilst surgery was not recommended in 11/46 patients with lesional epilepsy due to bilateral or widespread hypometabolism. 25 patients subsequently underwent epilepsy surgery, with 16/25 becoming seizure free following surgery.

Conclusion: ^{18}F-FDG-PET/CT has an added benefit for the localization and lateralization of EF, particularly in patients with normal or inconclusive MRI.

KEYWORDS:
Focal seizures, Lateralization, Malaysia, MRI negative epilepsy, Positron emission tomography

INTRODUCTION

Epilepsy is a common chronic neurological disorder, with prevalence of lifetime epilepsy is estimated at 7.8 per 1000 persons in Malaysia.[1] For the majority of people with epilepsy, seizures is controlled with medication but 30% of patients will continue to have seizures despite appropriate medication, thus posing significant burden to the patient, their families and to the overall healthcare system. Drug resistant epilepsy (DRE) in children is defined as seizures persisting despite maximally tolerated doses of at least two appropriately chosen anti-epileptic drugs (AEDs), with an average frequency of one seizure per month, for more than 18 months and less than 3 months of seizure free period during these 18 months.[2] The percentage of children with drug resistant epilepsy seen in the neurology clinic of the Paediatric Institute, Hospital Kuala Lumpur was reported at 45%. This figure likely reflects its' function as a tertiary referral centre.[3]

The diagnosis and management of DRE is essential, given the adverse effect of recurrent seizures on early brain development, learning, memory and neurological outcome. For some well selected children, the definitive treatment is for the surgical excision of the cortical area of ictal onset and initial seizure propagation, which is known as the epileptogenic focus (EF) or zone.[4] Young children with DRE and surgically remediable lesions are considered good candidates for aggressive surgical treatment due to the fact that they have increased neuroplasticity of the developing brain, hence the ability for better recovery post-surgery.[5-7] Furthermore, early surgical intervention with successful resection of EF will give satisfactory long-term social, psychologic and cognitive development.[6,7] A recent meta-analysis on paediatric epilepsy surgery confirmed that epilepsy surgery was more effective than medical therapy to control seizures.[8]

Pre-surgical evaluation aims to localize precisely the EF, to optimise seizure-free outcome and minimise unnecessary brain tissue resection, which may contribute to neurological deficits in a growing child. Brain magnetic resonance imaging (MRI) and scalp video electroencephalography (EEG) monitoring (VEM) are crucial to lateralize and localize

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the EF as well as ascertain the candidacy for surgery in refractory seizures.[4] Patients with clear lesions on MRI and concordant scalp EEG findings require no further investigations. However, additional investigations may be required when there are no lesions discernible on MRI (non-lesional epilepsy) or when there is discordant or inconclusive MRI and video EEG findings.[9]

Currently, the 'gold standard' of pre-surgical localisation of the EF and functional cortex is intracranial electroencephalogram (iCEEG). iCEEG has high sensitivity and specificity compared to scalp EEG, but is invasive, sample-limited, costly and risky with potential complications such as subdural, intracranial haematomas, bleeding, and osteomyelitis/infections.[10] Therefore, other non-invasive tools have been used to help with localisation of the EF, including ^{18}F-FDG PET/CT, single photon emission CT (SPECT) and magnetoencephalography (MEG).[9]

^{18}F-FDG PET/CT can provide an assessment of the physiological and pathophysiological processes in patients by measuring the molecular and biochemical changes that occur in the brain prior to the onset of structural changes, which may not be easily discernible on computed tomography (CT) and MRI. The measurement of cerebral glucose metabolism acts as a surrogate biomarker of neuronal pathology in various neurology disease conditions including dementia.[11] As healthy brain cells highly metabolise glucose, they avidly take up ^{18}F-FDG, which is a glucose analog.[12] However in DRE, ^{18}F-FDG uptake is reduced in affected brain regions, thus focal or diffuse hypometabolism is observed. Regions of hypometabolism of ^{18}F-FDG on PET/CT scans have been significantly correlated with regions of almost continuous epileptiform discharges on iCEEG and often concordant with histopathological examination (HPE) results of cortical malformative tissue.[13] ^{18}F-FDG PET/CT is therefore useful for determining the suitability of the patients to undergo surgery - especially if the children have normal or inconclusive MRI, bilateral lesions or when there are discordant results in the foci detected by scalp EEG and MRI.[14] However, the role of ^{18}F-FDG PET/CT in the clinical management of paediatric DRE has yet to be established as a standard of care in Malaysia.

Thus, the aim of this study was to identify whether ^{18}F-FDG-PET/CT has an added benefit for the detection of EF in DRE compared with MRI and scalp EEG in patients with normal MRI. We also assessed the detection rate of EF on ^{18}F-FDG-PET/CT as evidenced by foci of hypometabolism in patients with inconclusive MRI or discordant data. We then identified the clinical factors that were significantly associated with the detection of foci of hypometabolism on ^{18}F-FDG-PET/CT in DRE patients in our institution.

MATERIALS AND METHODS

Study design and subject recruitment

A cross-sectional study was conducted among 119 paediatric patients (aged 18 years and less) with DRE who were referred for ^{18}F-FDG-PET/CT from October 2015 to November 2016 at the National Cancer Institute, Putrajaya, Malaysia. The diagnosis of refractory epilepsy was made by the respective paediatric neurologists based on the consensus by the International league Against Epilepsy (ILAE) Commission on Therapeutic Strategies.[15] The medical records of all patients were reviewed. Important clinical information such as demographic data, age of seizure onset, duration and frequency of seizures, seizure type, the number of AEDs taken, the presence of developmental delay or autism, as well as information as to whether surgical intervention was performed were recorded and entered in the database. All patients underwent Video EEG Monitoring (VEM) and MRI brain as pre-surgical evaluation of DRE. Only patients with normal or inconclusive MRI were subjected to an ^{18}F-FDG-PET/CT scan.

Video electroencephalography (EEG) monitoring (VEM)

All 119 patients underwent scalp VEM using the 10-20 system at the same centre. Ictal and interictal events were reviewed and interpreted by trained neurologists, and categorized into normal, focal, lateralised or bilateral/poorly localised epileptiform patterns.

Magnetic resonance imaging (MRI) of the brain

MRI scans were performed using a 1.5T Ingenia (Philips, Amsterdam, Netherlands) scanner using the institutional standard epilepsy protocol. The MRI scans of the recruited study subjects were dichotomised into normal or lesional but inconclusive MRI. An inconclusive MRI scan was defined as either i) having discordance with the EEG results, ii) focal or unilateral MRI detected lesions with subtle changes and unclear margins, or iii) multiple or bilateral cerebral lesions.

^{18}F-FDG PET/CT scan protocol

Informed consent was sought from parents of patients prior to performing the ^{18}F-FDG PET/CT scan. The parents signed the parental agreement form after receiving an explanation regarding the procedure. The patients were required to be fasted for 4-6 hours prior to the scan. Anti-epileptic drugs were continued on the day of the examination.

Fasting blood sugar (FBS) level was checked on the day of the examination. The acceptable range of the FBS was 4 to 10mmol/L. The patients were then administered with 6MBq/kg of ^{18}F-FDG intravenously and directed to lie still with their eyes open in a quiet and dimly lit room. Hydration and urination were encouraged to reduced radiation exposure to radiosensitive organs and excessive activity was discouraged. Sedation using chloral hydrate or intravenous midazolam was given to children less than three years old or uncooperative children by the accompanied doctor prior to scan acquisition and ensured continuous cardiac monitoring. The image acquisition began with CT scan imaging for the purpose of attenuation correction and anatomical localisation, using a low dose of 140 kV and 180mA. This was followed by standard PET acquisition using a Discovery ST (General Electric Company (GE), Boston, USA) scanner, which had an intrinsic resolution of 20 mm in full width at half maximum (FWHM). The emission image was acquired for 25 minutes with a two-dimensional acquisition mode (2D), 60 minutes after the radiotracer injection. Slices of the trans-axial brain images were reconstructed using a filtered back-projection method. The reconstructed images were corrected for attenuation using attenuation maps. The trans-axial

images were then realigned to yield sagittal and coronal images.

^{18}F-FDG PET/CT image interpretation and analysis
Two senior nuclear medicine physicians visually assessed the regional ^{18}F-FDG metabolism seen on the scans by consensus. The visualized hypometabolic region(s) on the ^{18}F-FDG-PET/CT scans were determined to be the EF. ^{18}F-FDG-PET/CT findings were divided into two categories, i.e., normal and abnormal. Normal denoted that there was homogeneously avid FDG metabolism throughout all the cortical regions. Abnormal was defined as localized or non-localized area(s) of FDG hypometabolism. The site of hypometabolism was categorized into focal unilobar, multilobar unilateral, bilateral or global. The site of hypometabolism was further categorized into three regions, namely temporal lobe, extra-temporal represented by the frontal, parietal and occipital lobes, and temporal-plus represented by temporal with extra-temporal lobe involvement. ^{18}F-FDG hypometabolism patterns were dichotomized to localized or lateralised versus not localized or lateralised when studying the associated factors. The patients were subsequently followed-up at the HKL epilepsy clinic to review their clinical data and decide on the further management of their condition by the treating physician.

Statistical analysis
Statistical analysis was performed using online Graphpad Quickcalcs software (https://www.graphpad.com/quickcalcs/). Descriptive analysis was used to display the demographic data and the pattern of ^{18}F-FDG hypometabolism. Various clinical factors associated with FDG hypometabolism were analysed using chi-square and Fisher's exact tests. A p value of < 0.05 was considered statistically significant.

RESULTS

Demographic and clinical data
The 119 patients who fulfilled the inclusion and exclusion criteria 74 males were and 45 females. Their ethnicity comprised of 68% Malays, 19% Chinese and 13% Indians. The age of patients at the time of ^{18}F-FDG-PET/CT study ranged from 1 to 18 years old with mean age of 10.3 years. The minimum and maximum ages of seizure onset were 0.8 and 13 years old, respectively (mean: 3.6 years old). The mean duration from seizure onset to the ^{18}F-FDG-PET/CT study was 6.7 years.

Focal seizure was the commonest seizure type, noted among 62 patients (52%). This was followed by focal seizures with secondary generalisation in 21 patients (18%), mixed seizure types (including spasms) in 21 patients (18%), generalized seizures in 8 patients (7%) and epileptic spasms as the only seizure type in 7 patients (5%). All had DRE, with 41% of patients experiencing daily seizures. 85 patients (74%) had developmental delay, learning disability, or autistic spectrum disorder.

There was no significant difference in the demographic and clinical features between patients with normal or abnormal MRI, except for epilepsy duration, which was slightly longer with patients with abnormal MRI (7.6 vs 6.1 years, p=0.047) (Table I).

MRI results and aetiology
Brain MRI did not show any clear lesions in 73 children (61%). 46 patients (39%) showed lesions on their MRI, with features of atrophy/ encephalomalacia in 15/46 patients (33%), presumed perinatal stroke in 9/46 (20%), cortical malformation in 15/46 (33%), hippocampal atrophy in 5/46 (11%), developmental tumour in one (2%) and Rasmussen encephalitis in one (2%) (Figure 1).

The aetiologies for the MRI lesions were judged to be acquired in 21 patients; consisting of hippocampal atrophy in five patients and sequelae of: traumatic/non-traumatic intracranial haemorrhage in 5 patients, neonatal hypoglycaemia in four patients, hypoxic-ischaemic injury in three patients, meningitis/encephalitis in two patients, hemiconvulsive-hemiplegic epilepsy syndrome and Rasmussen encephalitis in one patient each. The aetiologies were judged to be congenital in 25 patients, consisting of presumed perinatal stroke in 9 patients, focal cortical dysplasia in 6 patients, multilobar dysplasia in 5 patients, hemispheric dysplasia in one patient, tuberous sclerosis complex in three patients and developmental tumour in one patient.

^{18}F-FDG PET/CT results
^{18}F-FDG PET hypometabolism was detected in 102 patients (86%), whereas the remaining 17 patients had normal 18F-FDG PET/CT scans. As for the site of 18F-FDG hypometabolism, the commonest type was the temporal-plus type (51%), followed by extra-temporal type (25%), and temporal-only type hypometabolism (24%). The pattern of distribution of ^{18}F-FDG hypometabolism in patients with normal MRI were focal unilobar in 16/73 (22%), multilobar unilateral in 8/73 (11%), bilateral in 27/73 (37%) and global in 5/73 (7%) of patients. The distribution of ^{18}F-FDG hypometabolism in patients with lesional MRI were focal unilobar in 8/46 (17%), multilobar unilateral in 22/46 (48%), bilateral in 14/46 (33%) and global in 2/46 (4%) of patients (Figure 2).

Factors associated with patterns of ^{18}F-FDG-PET/CT hypometabolism
In patients with no lesions on their MRI, localised or lateralised ^{18}F-FDG PET/CT hypometabolism were significantly associated with lateralised seizure semiology and focal or lateralised interictal EEG abnormalities. Young age (less than three years) at seizure onset and presence of developmental delay, learning disability or autistic features were associated with a non-lateralised PET hypometabolism. In patients with lesions on their MRI, localised or lateralised pattern of ^{18}F-FDG PET/CT hypometabolism concordant with the lesions were associated with localised/lateralised EEG abnormalities and congenital (as opposed to acquired) lesions (Table II).

Impact of ^{18}F-FDG PET/CT findings on decision-making for surgical intervention
Overall, the addition of ^{18}F-FDG PET/CT assessment, impacted 66 (55%) of the patients; 24/73 with non-lesional and 30/46

Table I: Comparison of demographic and clinical data between patients with normal and lesional MRI (AEDs=anti-epileptic drugs, DD= developmental delay, LD=learning disability, ASD=autistic spectrum disorder, SD=standard deviation)

	Total (n=119)	Normal MRI (n=73)	INCONCLUSIVE MRI (n=46)	P value
Sex				
Male	75	45	30	
Female	44	28	16	
Ethnicity				
Malay	70	45	25	
Chinese	30	16	14	
Indian	19	12	07	
Mean age seizure onset in years (SD)	3.6 (3.52)	3.9 (3.58)	3.3 (3.57)	0.410
Mean age at PET in years (SD)	10.3 (4.97)	9.9 (4.70)	10.8 (5.37)	0.328
Mean epilepsy duration in years (SD)	6.7 (3.96)	6.1 (3.52)	7.6 (4.47)	0.047*
Seizure frequency				
Daily (%)	49	29 (59%)	20 (41%)	0.706
Weekly (%)	36	27 (75%)	9 (25%)	0.064
Monthly (%)	34	17 (50%)	17 (50%)	0.14
Mean number of current AEDs (SD)	2.3 (0.79)	2.2 (0.77)	2.4 (0.80)	0.226

Table II: Factors associated with focal/ lateralised versus non-lateralised ^{18}F -FDG PET hypometabolism (EEG= electroencephalogram, AEDs=anti-epileptic drugs, DD= developmental delay, LD=learning disability, ASD=autistic spectrum disorder). **Ictal EEG only for 55/73 patients with normal MRI, and 36/46 with inconclusive MRI.

		Normal MRI (n=73)				inconclusive MRI (n=46)			
		Focal/ lateralised PET (n=24)	Non-lateralised PET (n=49)	Total	P value	Focal/ lateralised PET (n=30)	Non-lateralised PET (n=16)	Total	P value
SEIZURE	Lateralised	13 (54%)	11 (46%)	24	0.009*	16 (76%)	5 (24%)	21	0.217
SEMIOLOGY	Not lateralised	11 (22%)	38 (78%)	49		14 (56%)	11 (44%)	25	
INTER-ICTAL	Focal/ lateralised	13 (50%)	13 (50%)	26	0.036*	22 (88%)	3 (12%)	25	0.031*
EEG	Not focal/ lateralised	11 (23%)	36 (77%)	47		8 (38%)	13 (62%)	21	
ICTAL EEG**	Focal/ lateralised	8 (36%)	14 (64%)	22	0.591	17 (81%)	4 (19%)	21	0.071
	Not focal/ lateralised	16 (29%)	39 (71%)	33		7 (47%)	8 (53%)	15	
SEIZURE ONSET	<3 yrs	7 (18%)	33 (82%)	40	0.003*	16 (57%)	12 (43%)	28	0.210
	>3 yrs	17(52%)	16 (48%)	33		14 (78%)	4 (22%)	18	
SEIZURE DURATION	<3 yrs	7 (18%)	33 (82%)	40	0.003*	16 (57%)	12 (43%)	28	0.210
	> 5 yrs	11 (28%)	28 (72%)	39		20 (67%)	10 (33%)	30	
SEIZURE FREQUENCY	Daily	6 (21%)	23 (79%)	29	0.082	11 (58%)	8 (42%)	19	0.531
	Weekly/ monthly	18 (41%)	26 (59%)	44		19 (70%)	8 (30%)	27	
AEDS	<2	6 (22%)	21 (78%)	27	0.198	14 (70%)	6 (30%)	20	0.756
	>2	18 (39%)	28 (61%)	46		16 (62%)	10 (38%)	26	
DD/LD/ASD	Yes	12 (24%)	37 (76%)	49	0.037*	24 (71%)	10 (29%)	34	0.292
	No	12 (50%)	12 (50%)	24		6 (50%)	6 (50%)	12	
LESION	Congenital	NA	NA			23 (82%)	5 (18%)	28	0.011*
	Acquired	NA	NA			7 (39%)	11 (61%)	18	

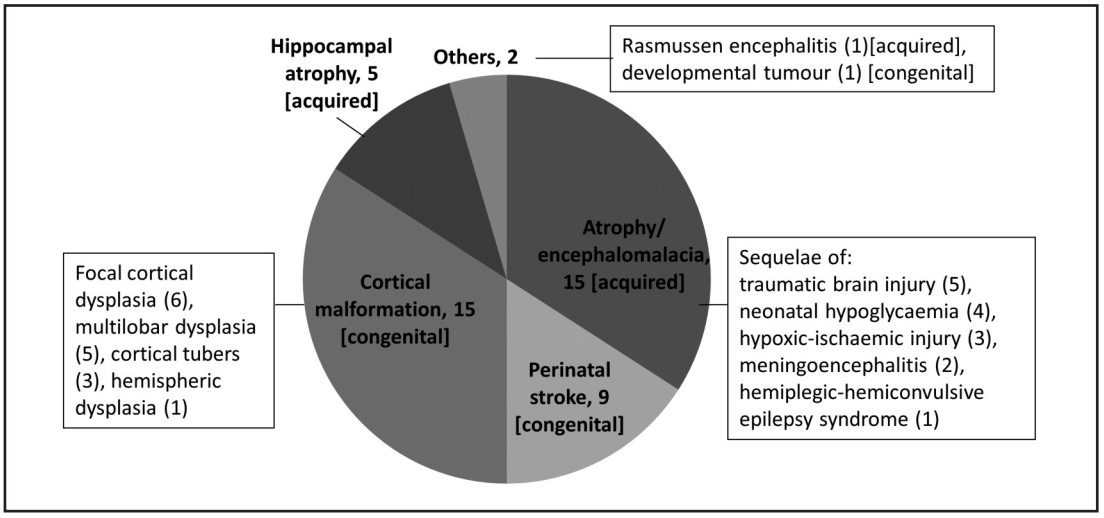

Fig. 1: MRI findings and aetiologies in patients with lesional epilepsy (n=46), classified into congenital (25/46) and acquired (21/46) categories.

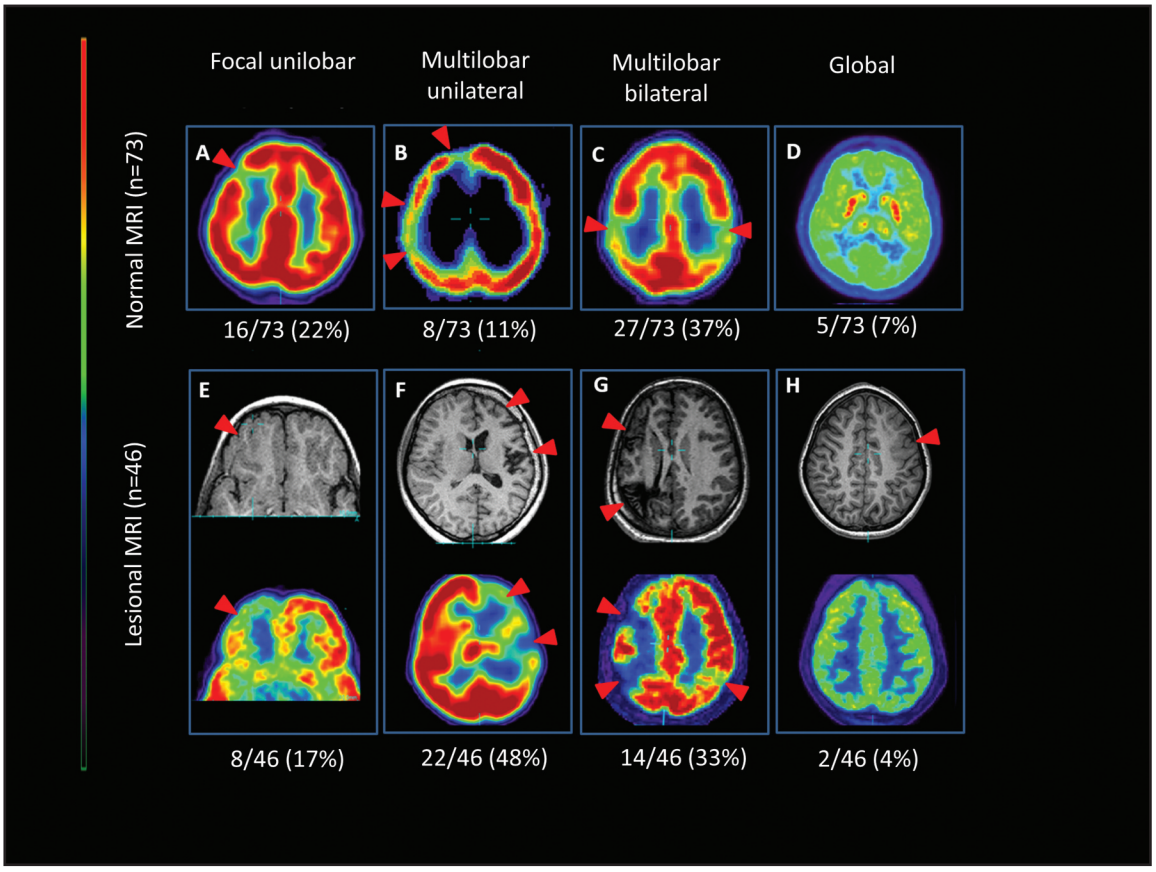

Fig. 1: Patterns of ^{18}F-FDG PET hypometabolism seen in 56/73 patients with normal MRI (top row, A-D) and all patients with lesional MRI (bottom row, E-H). (E) T1-weighted axial MRI showing abnormal grey-white differentiation over the right orbitofrontal region and concordant focal hypometabolism, suggestive of focal cortical dysplasia, (F) T1-weighted axial MRI showing left frontotemporal atrophy in a patient with traumatic brain injury and concordant hypometabolism, (G) T1-weighted axial MRI shows multilobar encephalomalacia involving the right hemisphere in a patient with history of HSV encephalitis – PET detected additional left parietal hypometabolism where no clear lesion was seen on the MRI, (H)) T1-weighted axial MRI showing thickened cortex and broad gyri in a patient with a poorly defined left frontal focal cortical dysplasia – PET was not helpful as it showed global hypometabolism.
Colour scale: red = highest level of ^{18}F-FDG uptake, dark blue/violet = lowest level of ^{18}F-FDG uptake. Red arrowheads denote areas of abnormalities.

patients with lesional epilepsies were recommended for surgery or further surgical work up, based on localised/ lateralised ^{18}F-FDG PET hypometabolism and concordant pre-surgical data. A total of 11/46 (24%) of patients with lesional epilepsy was not recommended for surgery due to bilateral or non-localising ^{18}F-FDG PET findings. A further 2 patients were recommended surgery despite non-concordant ^{18}F-FDG PET findings; one boy with a left frontal dysplasia who showed global hypometabolism (likely due to frequent seizures prior to the ^{18}F-FDG PET/CT scan) and another with left temporal dysplasia who showed bilateral temporal hypometabolism. The ^{18}F-FDG PET/CT scan findings in the rest of the patients recruited in this study did not significantly influence the decision-making for surgery.

At the time of analysis, 25 patients (including 7 with no clear lesions on the MRI) underwent epilepsy surgery. Seven and 2 patients had frontal and parietal lesionectomies respectively, assisted by intra-operative electrocorticographic monitoring, whilst one had an extensive resection of a parieto-occipital tuber. Eight patients had anterior temporal lobectomies, including one who had an additional frontal resection. Functional hemispherotomy was performed in 4 patients and temporo-parieto-occipital disconnection in 3 patients.

16/25 patients (64%) remained seizure-free, achieving Engel class I surgical outcome after a median follow-up of 20 months post-operatively. In contrast, only 13/94 (14%) patients who were continued on AED medical therapy were seizure-free. Histopathology of five out of seven patients with normal MRI who had surgery revealed cortical dysplasia.

DISCUSSION

We were able to show that in Malaysia, ^{18}F-FDG PET/CT provided useful additional information in patients with DRE who were being considered for epilepsy surgery. In patients with DRE and normal MRI, localised or lateralised ^{18}F-FDG PET hypometabolism indicative of the EF was seen in 24/73 (33%) of patients. In patients with DRE and poorly defined MRI lesions or discordant pre-surgical data, concordant hypometabolism and MRI abnormality was seen in 30/46 (65%) of patients, whilst confirmation of bilateral abnormalities was observed in 11/46 (24%) of patients. Thus overall, addition of ^{18}F-FDG PET/CT investigation impact on more than half of the patients in our cohort (65/119, 55%), allowing for greater confidence in the selection and rejection of epilepsy surgery candidates.

The utility of interictal ^{18}F-FDG PET/CT as a tool for localization and lateralization of seizure focus has been demonstrated by many previous studies.[13,16,18] The reported sensitivity of ^{18}F-FDG PET/CT for identifying seizure focus ranged from 45-90%, with generally higher sensitivity in temporal versus extratemporal foci.[16] It is particularly useful for detection of hypometabolic area in a subtle cortical dysplasia which may not be apparent on standard MRI imaging, and showed good correlation with intracranial EEG and histopathology findings. The role of ^{18}F-FDG PET/CT in the pre-surgical evaluation of refractory epilepsy in Malaysia has been explored by Lim et al., in 2017.[17] In that study, 13/16 patients who underwent stage two evaluation for epilepsy surgery had ^{18}F-FDG PET/CT scan – at least 5/13 patients had cortical dysplasia confirmed on histopathology; however the concordance between ^{18}F-FDG PET/CT and other investigative modalities was not stated. In our study, histopathology confirmed focal cortical dysplasia in 71% of patients with normal MRI and focal ^{18}F-FDG PET hypometabolism who underwent epilepsy surgery. A total of 16 patients became seizure free following surgery, with others experiencing variable degrees of seizure reduction, suggesting correct ^{18}F-FDG PET and MRI identified EF in the majority of patients. Not surprisingly, we found that lateralised seizure semiology (evidence of clinical seizure starting on side of the body) and focal/ lateralised interictal EEG abnormalities were associated with concordant focal/ lateralised ^{18}F-FDG PET hypometabolism.

In our experience, not only was ^{18}F-FDG PET/CT useful in detecting focal areas for resection, it was also useful to look for hypometabolism in the regions outside the presumed EF, the presence of which would make one cautious about recommending epilepsy surgery. It should be noted however, that a significant number of patients in our study, both with or without MRI lesions, showed bilateral ^{18}F-FDG PET hypometabolism. ^{18}F-FDG PET hypometabolism beyond the epileptogenic foci may reflect seizure propagation, for example, the spread of ^{18}F-FDG PET/CT abnormalities in patients with temporal lobe epilepsy (TLE), that extend beyond the anterior and mesial regions, was observed in 32% of TLE patients.[18] Hypometabolism in other cortical regions may also be observed due to presence of independent EF that may not apparent on brain MRI.[19] Additionally, other clinical factors may contribute to ^{18}F-FDG PET hypometabolism, such as presence of development delay and learning disability[20], anti-epileptic medications (especially phenobarbitone), duration of seizures and specific epilepsy or genetic syndromes.[19] In our study, young age (less than 3 years) at seizure onset (but not seizure duration), acquired lesions (as opposed to congenital lesions) and presence of developmental delay, learning disability or autism, were associated with bilateral ^{18}F-FDG PET hypometabolism.

Technical factors may also influence the degree and diagnostic accuracy of ^{18}F-FDG PET/CT study in DRE. It is mandatory to ascertain recent episodes of seizures prior to ^{18}F-FDG PET study – seizures just prior to or during acquisition may increase the influx of glucose into the EF, which may in turn result in contrary ^{18}F-FDG PET hypermetabolism instead of hypometabolism.[21] Adherence to pre-injection preparations such as optimal fasting of at least 4-6 hours will reduce endogenous insulin excretion and ensure optimal FDG uptake into the brain cells. Lying quietly with eyes closed in dimly lit room with avoidance of activities like reading, talking or listening few minutes before and during uptake time will prevent increase of FDG metabolism in visual, language-motor cortical as well as auditory areas. During image acquisition, careful precaution must be made to avoid head movement by using a head rest and reminding older children to avoid voluntary movements of head as much as possible. Presence of motion artifact may compromise the image quality and interpretation. In certain patients requiring sedation, careful attention to timing of sedation is crucial. Sedation must not be given too early or too close

(within 20 minutes) to FDG injection as it may interfere with FDG metabolism and biodistribution in the brain, leading to erroneous findings.[22,23]

There are currently 21 centres in Malaysia with dedicated PET-CT scanners offering their services mainly for oncological cases. To date, only two government hospitals, one university hospital and four private hospitals in Malaysia are offering ^{18}F-FDG-PET/CT for neurological studies, specifically epilepsy. The limited use of ^{18}F-FDG PET/CT imaging for epilepsy investigation is probably partly due to the low request for such imaging from the treating neurologists. Furthermore, not many nuclear medicine specialists in Malaysia are well-versed with ^{18}F-FDG PET/CT imaging interpretation and reporting in cases of epilepsy. The relatively higher cost (compared to MRI) and radiation exposure may also limit its' routine use in evaluation of patients with DRE. At the same time, improvement in MRI quality have improved lesion detection and may obviate the need for ^{18}F-FDG PET/CT scan for some patients with DRE.[9]

The limitation of this study is our resources, in which we were unable to utilise any neurology image processing software in order to perform a semi-quantitative assessment to identify epileptogenic foci. Semi-quantitative assessment using voxel-based analysis with statistical parametric mapping or three-dimensional stereotactic surface projection sequence such as Neurostat is an important tool that have been proven to have added benefit to the physician in the interpretation of the area of hypometabolism for epileptic focus detection.[24] Moreover, our subjects were children in which there is no establishment of control database for this age group. We recommend that future studies should deploy the semi-quantitative processing software methods to improve the diagnostic accuracy of ^{18}F-FDG PET/CT in drug resistant epilepsy.

CONCLUSION

^{18}F-FDG-PET/CT is a non-invasive, neuroimaging tools that can improve the detection of EF in DRE, especially in patients with normal or inconclusive MRI and clinical data. Recognition of the indications and limitations of this important imaging modality may improve the care of patients with DRE in Malaysia.

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