THE ROLE OF ^{18}FLUORINE-FLUORODEOXYGLUCOSE PET/CT IN PRE-SURGICAL EVALUATION OF PAEDIATRIC EPILEPSY

By

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^{18}F	^{18}Fluorine
FDG	Fluorodeoxyglucose
PET	Positron Emission Tomography
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
EEG	Electroencephalogram
iCEEG	Intracranial EEG
SPECT	Single Photon Emission Computed Tomography
AEDs	Anti-epileptic drugs
kEV	Kiloelectronvolt
TLE	Temporal lobe epilepsy
ILAE	International League Against Epilepsy
T	Tesla
FLAIR	Fluid-attenuated inversion recovery
SUV	Standard Uptake Value
GTC	Generalized tonic clonic

Abstrak

Pengenalan: Kira-kira 10 – 40% pesakit kanak-kanak yang menghidap epilepsi terus menderita serangan sawan walaupun terapi perubatan telah dimaksimumkan. Keadaan inin dikenali sebagai Epilepsi Refraktori.

Objektif: Untuk menilai peranan ^{18}F-FDG-PET/CT sebagai pengimejan neuro tidak invasif yang bermanafaat dalam penilaian pra-pembedahan pesakit epilepsi refraktori pediatrik.

Metodologi: Ini ialah satu kajian keratan rentas. Seramai 119 pesakit yang berumur dari 1 hingga 18 tahun dan menghidap epilepsi refraktori antara Jun 2013 sehingga Mei 2016 terbabit dalam kajian ini. Kriteria pemilihan untuk kajian ini ialah pesakit mempunyai keputusan MRI yang normal atau tidak konklusif. Pesakit telah terlebih dahulu menjalani penilaian pra-pembedahan lain seperti video EEG dan MRI otak sebelum ujian ^{18}F-FDG-PET/CT. Keupayaan untuk ^{18}F-FDG-PET/CT mengesan FDG hipometabolisme dinilai dan dibandingkan dengan EEG dan MRI. Faktor-faktor klinikal yang mempengaruhi hipometabolisme juga dinilai.

Keputusan: Majoriti pesakit di dalam kajian ini adalah terdiri daripada etnik Melayu dan lelaki. ^{18}F-FDG-PET/CT telah mengesan hipometabolisme seramai 100 pesakit (84%). ^{18}F-FDG-PET/CT mengesahkan lokalisasi dalam 30/48 (63%) yang mempunyai unifokal dan lateralizasi di dalam discaj EEG. Terdapat persetujuan ketara di antara MRI dan ^{18}F-FDG-PET/CT ($p= 0.001$) untuk pesakit yang mempunyai MRI inkonklusif di mana FDG-

PET melokasikan hipometabolisme in 45 patients (98%). PET mengesahkan lokalisasi dalam 26/46 pesakit (57%) yang mempunyai lesi MRI. 55/73 pesakit (75%) yang mempunyai MRI yang normal menunjukkan FDG hipometabolisme. Jantina pesakit merupakan faktor klinikal tunggal yang menunjukkan persetujuan ketara dengan FDG hipometabolisme ($p = 0.049$).

Kesimpulan: ^{18}F-FDG-PET/CT didapati merupakan satu pengimejan neuro tidak invasive yang amat berguna di dalam penilaaian pra-pembedahan bagi pesakit epilepsi di kalangan kanak-kanak. Kadar pengesanan FDG hipometabolisme dan kadar lokalisasi dan lateralizasi fokus epilepsi ialah tinggi terutamanya untuk pesakit yang mempunyai MRI yang normal dan tidak konklusif.

Abstract

Introduction: Approximately 10–40% of paediatric epilepsy patient will continue to suffer from debilitating seizures despite optimization of medical therapy. This is known as refractory epilepsy.

Objective: To assess the role of ^{18}F-FDG-PET/CT as a non-invasive functional neuroimaging in pre-surgical evaluation of refractory paediatric epilepsy.

Methodology: This was a cross-sectional study. A total of 119 patients with age ranging from 1 till 18 years old who were diagnosed as refractory epilepsy between the period of Jun 2013 till May 2016 were included in this study. The inclusion criteria include refractory epilepsy with normal or inconclusive MRI. Patients underwent pre-surgical evaluation such as video EEG and MRI brain prior to ^{18}F-FDG-PET/CT. Ability of ^{18}F-FDG-PET/CT to detect FDG hypometabolism was evaluated and compared to scalp EEG and MRI. The factors affecting hypometabolism were also assessed.

Result: There were predominant Malay ethnic and male patients in our subjects. ^{18}F-FDG-PET/CT detected hypometabolism in 100 patients (84%). The pattern of FDG hypometabolism being highest is bilateral multifocal in 45%.^{18}F-FDG-PET/CT confirmed localisation in 30/48 (63%) with unifocal and lateralized EEG discharges. There is a significant agreement between MRI and ^{18}F-FDG-PET/CT ($p= 0.001$) in patients with inconclusive MRI where FDG-PET localized hypometabolism in 45 patients (98%). PET confirmed localisation in 26/46 children (57%) with lesional epilepsies on MRI. 55/73 children (75%) with normal MRI showed FDG hypometabolism. Gender is

the only clinical factors which shows significant association with FDG hypometabolisms ($p = 0.049$).

Conclusion: ^{18}F-FDG-PET/CT found to be a useful non-invasive neuroimaging tools in presurgical evaluation of refractory epilepsy in paediatric patients. FDG-PET/CT shows higher detection rate as well as localization and lateralization of seizure foci especially in a patients with normal MRI or inconclusive MRI.

CHAPTER 1

INTRODUCTION

1.1 Epilepsy, prevalence and incidence

Epilepsy is one of the chronic brain disorders resulting from long lasting predisposition characterized mainly by excessive and unprovoked interruption of normal brain function generating an epileptic seizure causing neurobiological, psychological, cognitive and social consequences. Epileptic seizure is a temporary occurrence of neurological signs and symptoms which occur more than one episode. It is a complex disease entity comprises variety of disorders reflecting brain dysfunction resulted from various aetiologies (Fisher *et al.*, 2005). World Health Organization (WHO) estimated 50 million of the whole population is affected by epilepsy with nearly 80% of patients came from low and middle-income countries like Malaysia. The prevalence of epilepsy is approximately 1% of the world population with an incidence of 70 per 100,000 peoples over one annum (Kazemi *et al.*, 2011).

In paediatric population, epilepsy is the most frequent neurological disorder which is long standing, and considered to be burdensome mentally and physically to both parents and affected children alike. Many descriptive epidemiology studies reported incidence of 35 to 128 per 100000 of paediatric population. Although various descriptive studies involving many countries have been done, the prevalence rate does not differ much approximately 3 to 10 per 1000 depending on the children age (Hauser, 2016). In other descriptive study, the annual incidence in children between the age 0-15 years old is 5-7 per 10000 (Salmenpera *et al.*, 2005).

1.2 Refractory epilepsy in paediatric

Despite the fact that most of epilepsy patient give a good respond on antiepileptic medications, there are approximately 10–40% of them that will continue to suffer from debilitating seizures although medical therapy has been maximized and known as refractory epilepsy (Desai *et al.*, 2013; Kazemi *et al.*, 2011; Patil *et al.*, 2007; Go & Snead, 2008). The definition of refractory epilepsy must be individualized to the children. The most common definition is when seizure persist in a child despite maximally tolerated doses of more than two anti-epileptic drugs (AEDs) with 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 (Berg *et al.*, 2006). Other factors apart from number of AEDs and duration of seizures that need to be put into considerations in the definition are intolerant to AEDs side effects, duration of unresponsiveness to AEDs, minimum frequency that needs to be considered to be refractory, epilepsy syndrome involved and patient's age at the time of seizure onset (Meador, 2002).

Diagnosis and management of refractory epilepsy in paediatric population is very important given the adverse effect of recurrent seizures on early brain development, learning, memory and adverse neurological outcome. In addition, young children with this refractory disorder may be good candidates for aggressive surgical treatment because of the increased neuroplasticity of the developing brain (Go & Snead, 2008). Furthermore, children with refractory epilepsy usually developed diagnostic and therapeutic challenge later in life, thus early surgical intervention with successful resection of epileptic zones will give satisfactory social, psychologic and cognitive development (Kumar *et al.*, 2010). Maton *et al.* (2008) in their cohort study involving 20 children aged less than 5 years old had proven that surgical resection for refractory epilepsy children gives advantage to large numbers of patients. Approximately 65% of their patients experienced seizure freedom

and 15% had improvement of seizure attack more than 90% after a mean follow-up of 5.5 years post-operatively.

1.3 Pre-surgical evaluation

In any institutions that offer an epilepsy surgery, a patient's eligibility for surgical intervention is determined after a full and comprehensive assessment carried out. Pre-surgical evaluation aims to looking for and ascertains the extent and specifies abnormal areas which believed to be a seizure focus. It is extremely important to localise precisely an epileptogenic focus to enhance the seizure outcome after resection of the involved region especially in focal cortical resection. Besides, this prevents any unnecessary brain tissue resection which may contribute to neurological deficits in a growing child. Multiple investigations are required to lateralize and localize the seizure focus and function in the brain as well as ascertain the candidacy of a child with refractory seizures (Kazemi *et al.*, 2011).

Localisation of the epileptic focus, risk stratification associated with surgery and estimation of functional neurological outcome post- surgery are the hallmark aims in the pre-surgical assessment of the patient. Correct identification of seizure focus with complete resection of the same focus is the key of successful surgery (Patil *et al.*, 2007). At present, pre-surgical localisation of the epileptogenic zone and functional cortex in non-lesional and extratemporal lobe epilepsies still relies largely on invasive intracranial electrodes. Intracranial electroencephalogram (iCEEG) has high sensitivity and space specificity compared to scalp EEG and it is still considering a gold standard for localisation the epileptogenic foci (Blount *et al.*, 2008). However, iCEEG is invasive, sample-limited, costly and risky with potential complications such as subdural,

intracranial hematomas, bleeding and infections (Blount *et al.*, 2008; Michel & Seeck, 2010).

Pre-surgical evaluations gather all available information from clinical history and examination, followed by interictal/ictal video and scalp electroencephalogram (EEG), and structural imaging with computed tomography (CT) or magnetic resonance imaging (MRI). Subsequently, it is followed by an assessment by a psychologist and a psychiatrist. High resolution MRI is important for precise localisation of structural abnormalities which can be possible site of seizure focus in ensuring a successful outcome post-surgery (Salmenpera *et al.,* 2005). Presence of structural abnormalities in MRI is integrated with EEG findings and children with concordant MRI and EEG could be subject to surgery in a proper clinical setting without requiring further investigations. However, when MRI fails to show any structural abnormalities like hippocampal sclerosis, is discordant with EEG finding or shows poor delineation of lesions, further studies with functional neuroimaging like single photon emission tomography (SPECT) or positron emission tomography (PET) should be done and, if necessary possibly with an iCEEG monitoring (Hirsch & Arzimanoglou, 2004).

In the past, before the availability of PET, SPECT was highly utilized for functional neuroimaging in epilepsy. However, for more than one decade, interictal PET using for ^{18}Fluorine-Fluorodeoxyglucose (^{18}F-FDG) is greatly utilized and plays an important role in providing additional localising information. In interictal PET, most of the time area of hypometabolism is strongly associated with origin of seizure focus (Casse *et al.,* 2002).

Thus, this study aim is to determine the role of ^{18}F-FDG PET/CT in the detection of seizure focus by looking at area of hypometabolism in children with refractory epilepsy referred from Epilepsy Clinic Institute Paediatric Hospital Kuala Lumpur as one of the pre-surgical evaluation. We also assess whether PET/CT is helpful in surgery decision by clinician and correlate its finding with EEG and MRI results. Several clinical factors which contributed to the FDG hypometabolism in PET/CT are also evaluated.

CHAPTER 2

LITERATURE REVIEW

2.1 Paediatric epilepsy, epidemiology, pathophysiology and refractory epilepsy

Epilepsy is characterized by epileptic seizure which is a temporary occurrence of signs and symptoms due to excessive and synchronous neuronal activity in the brain (Fisher *et al.,* 2014). Paediatric epilepsy is a common and chronic phenomenon, often troublesome to parents and affected children alike. During early infancy and childhood period, rapid brain development is responsible for a complex evolution of clinical seizure semiology, electroencephalographic, and neuroimaging findings (Cowan, 2002). There are various incidence and prevalence available in many studies. Bergin (2003) shows that a yearly incidence of paediatric epilepsy is about 40 of 100,000 in the first decade of life. In one extensive epidemiology review, the average incidence of paediatric epilepsy rates across populations is equivalent, ranging between 50-72 per 100,000 annually despite various methods of epidemiological research (Cowan, 2002). Mac *et al.* (2007) in a systematic review of prevalence in Asian countries reported low prevalence in the whole populations; however, there is peak prevalence in paediatric age group compared to adult.

Although the pathophysiology of epilepsy is debatable the finding noted in experimental models indicates that any initial precipitating event such as status epilepticus or prolonged febrile seizures resulted in inflammatory processes which may precede the onset of epilepsy in humans (Vezzani, 2014). Several other factors which may contribute to pathophysiology of seizure in children is birth brain injury (hemorrhage, stroke, infection, hypoxia), abnormal brain or cortical development and gene mutations (Hauser, 2016).

Previously, aetiology of epilepsy is divided into idiopathic, cryptogenic, and symptomatic. In 2010, International League Against Epilepsy (ILAE) has recommended a new terminology and concepts for aetiology and types of seizure. The classifications of aetiology are divided into genetic, structural/metabolic and unknown. Genetic epilepsy is

describe as known or presumed genetic cause in which seizures is the core symptoms of disorder. A specific molecular genetic studies or the evidence for a central role of a genetic component from appropriately designed family studies is carried out to determine the genetic cause. Structural/metabolic epilepsy in the other hand is a distinct other structural or metabolic condition or disease that has been proved to be associated with a substantially increased risk of developing epilepsy in appropriately designed studies. Acquired disorders such as stroke, trauma, hypoxia and infection are included in this structural lesion. However, the entity of epilepsy with genetic cause difficult to be separated. Thus structural/metabolic epilepsy may overlapped with genetic origin (i.e: tuberous sclerosis, cerebral malformations) (Berg *et al.,* 2010).

The clinical presentation and seizure types are different in each individual. In the new classification, ILAE divided seizure types into focal seizure, generalized seizure as well as spasm (Berg *et al.,* 2010; Camfield & Camfield, 2015). Generalized epileptic seizures are conceptualized as arising at some point within, and rapidly engaging, distributed networks bilaterally. Cortical and subcortical structures can be included in both networks, but do not necessarily include the entire cortex. Focal epileptic seizures are conceptualized as arising within networks limited to one hemisphere. They may be discretely localized or more widely distributed. It may originate in subcortical structures. In 1981, ILAE classification of seizure, spasms were not clearly acknowledged but since 2010, they are included. The term epileptic spasms was formerly known as infantile spasms (Blume *et al.,* 2001). There was inadequate knowledge to make a firm decision regarding whether spasms should be classified as focal, generalized, or both; consequently, they have been placed in their own group as unknown (Berg *et al.,* 2010). Two studies in two different countries have shown dominant type of seizures in their patients were 68% and 50% respectively (Wirrel *et al.,* 2011; Durá-Travé *et al.*, 2008).

Anti-epileptic drug (AED) remains the first line therapy choice for paediatric epilepsy patients. In view of that, selection of AED for initial therapy must be individualized based upon clinical judgment and patient-specific circumstances, such as the specific epilepsy syndrome, anticipated duration of treatment, underlying comorbidities and overall cost effectiveness. In focal seizure, oxcarbazepine is among the first-line treatment. For generalized epilepsies, the AED choice is highly dependent upon which specific syndrome is being treated. In generalized epilepsy with primary absence seizures, lamotrigine is the most common AED of first choice. The aim of epilepsy treatment is single drug therapy because this is associated with good compliance, fewer side effects, and lower cost. When the seizure resistant or adverse reactions occurred with first AED, a second AED is introduced. Majority of patients with newly diagnosed epilepsy showed favourable response with their first AED or second regimen (Malphrus & Wilfong, 2007).

Mohanraj and Broodie (2006) proved that 31.4% of their study population never had relapsed after taking the first dose of AEDs. Concurrently, there were approximately 25 to 30 % of patients seem to be resistant to pharmacological therapies in other studies and were regarded as refractory epilepsy (Hauser *et al.,* 2001; Sander, 1993). In 2010, the ILAE has proposed that refractory epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom (Kwan et al., 2010). Refractory epilepsy in children is defined as children with seizures that are uncurbed (i.e., failure of two or three appropriate drugs) or are disabled (including medication side effects) by the medical treatment (Cross *et al.,* 2006). In children, various factors need to be considered in a definition of refractory epilepsy including the number of AED failures, minimum frequency at which seizures must occur to be considered

refractory (daily, monthly, and so forth), duration of unresponsiveness to medication, epilepsy syndrome involved, cause of seizures in the absence of a clear-cut epilepsy syndrome, and patient age at the onset of seizures (Berg, 2005). Once patient is clearly defined as having refractory epilepsy, the clinicians are suggested to consider other modalities, including vagus nerve stimulation, ketogenic diet and also epilepsy surgery (Malphrus & Wilfong, 2007).

2.2 Pre-surgical evaluation of refractory epilepsy

In children with refractory epilepsy early surgical intervention is important as long term seizure attack and AEDs usage may cause unwanted effects on a children's cognitive function and psychosocial development (Aldenkamp & Arends, 2004). Due to inherent functional plasticity of the growing brain in children, the expected post-surgery outcome on brain development is favourable (Devlin *et al.,* 2003).

Seizure-free status with no obvious neurologic deficit is a hallmark aims of successful outcome in epilepsy surgery. Precise localisation of epileptogenic zone and determination of anatomic location of eloquent cortex in the brain with aim to spare these areas during planned surgical excision are two important pre-requisites prior to surgery to achieve these outcome (Snead, 2001). The iCEEG can guide a surgeon to achieve the successful outcome, but it is invasive, and less cost-effective. Other than that, there is no definite non-invasive diagnostic test that can be dependable on to achieve the outcome. Thus, cumulative findings in lateralizing and localizing the epileptogenic zone from multiple tests are needed to identify its concordance and agreement as well as ascertain the candidacy of a child with refractory seizures for surgery (Go & Snead, 2008).

To achieve this goal, referral to tertiary centre for pre-surgical evaluation is compulsory. The patients' eligibility for surgery includes history and physical examination, long term video/scalp EEG, anatomical imaging such as CT scan and MRI, and also functional imaging such as ^{18}F-FDG-PET/CT, neurophysiological and neuropsychiatry assessment (Cross *et al.,* 2006). All of these information was subsequently gathered and further discussed by committee of multidisciplinary team includes neurologist, nuclear medicine physician, radiologist, psychiatrist and surgeon (Cross *et al.,* 2006).

In all refractory epilepsy patients, long term scalp/video- EEG monitoring remains the first line investigation to localize and lateralized the site of seizure origin as well as documenting an ictal seizure and seizure semiology. Various methods such as adjustment of AEDs and sleep deprivation is usually done to stimulate the seizure. However, it requires longer hospital stays, trained staff/nursing personnel, family's cooperation and high cost. It also has technical limitations such as restricted potential fields to record as it need a large volume of cortex displaying a synchronous electrographic activity as well as inadequate recording of the deeper cortical areas such as mesial temporal and occipital cortex (Keene & Ventureyra, 2000; Go & Snead, 2008).

CT scans of the head with and without contrast also are utilized in a pre-surgical evaluation. However, the use of it is currently largely replaced with high resolution MRI. CT can demonstrate large destructive lesions or infarction. However, it has limited abilities in the detection of low-grade neoplasms, cortical dysplasia, and cavernous hemangiomas. Furthermore, technical issues such as lower cuts of the middle fossa being obscured by bony artefacts, and a risk of exposure to ionizing radiation as well as potential risk of allergy to contrast material to the patients (Keene & Ventureyra, 2000).

MRI has superior resolution for soft tissues compared to CT. Currently, it remains the imaging of choice for depicting structural lesions such as hippocampal sclerosis, cerebral malformations as well as change in T2-weighted signal intensity (Dupont & Baulac, 2004). To increased sensitivity of detection and apparent localization of lesion, MRI should be done in high field equipment (1.5 or 3.0 Tesla, T) following a standard protocol for epilepsy including the 3D, T1-weighted, T2-weighted, FLAIR (fluid-attenuated inversion recovery pulse) and the gradient echo sequences (Setoain *et al.,* 2014). In one study, high resolution MRI using 3.0T machine with epilepsy protocols shows ability of MRI to localise apparent lesion in 86% of their subjects. However, the study concluded that the rest of 24% subjects with normal MRI could have a mild cortical dysplasia or microdysgenesis represented the majority of the pathological substrates missed by MRI (Kassem *et al.,* 2013). Another study found majority of the patients with normal MRI has neuronal migration disorder on histopathological examination which includes mild cortical dysplasia (Hwang *et al.,* 2001).

When MRI is normal or focal/unilateral lesions detected is discordant with EEG findings, has unclear margins or multiple lesions detected, functional imaging such as ictal SPECT and inter-ictal PET plays an important role. Use of functional imaging in MRI normal group especially has been shown to fewer the uses of iCEEG recordings to localise the seizure focus.

SPECT is used to assess cerebral blood flow changes during the ictal periods because of the short uptake time of the radiotracer (Hwang *et al.,* 2001). The common tracers used to assess regional cerebral blood flow are hexamethylpropylenamine (HMPAO) and ethyl cysteinate dimer (ECD) tagged with metastable technetium-99 (^{99m}Tc). Both tracers are small-sized lipophilic compounds which are transformed into a neutral charged hydrophilic compound after crossing the blood brain barrier, fixed

irreversibly with no redistribution (Ziessman *et al.*, 2013;Setoain *et al.*, 2014). In the ictal state, active focus shows increased tracer activity representing increased regional cerebral blood flow. However, SPECT requires hospital admission and withdrawal of AEDs to stimulate seizure. Once seizure attack occurred, trained personnel must inject the radiotracer within seconds of seizure onset. Delayed imaging is possible given the patients' cooperation with imaging in a reasonable time frame. Ictal SPECT study has a sensitivity of nearly 90% in temporal lobe seizures, with sensitivity of 50% to 75% in extra-temporal lobe seizures. Normally, the abnormal areas detected in ictal SPECT are generally larger than any structural abnormality detected from MRI (Ziessman *et al.*, 2013). Hwang *et al.* (2001) shows overall correct localization rate of ictal SPECT is 70.3% regardless of lesion location.

Large number of studies has demonstrated that FDG-PET is highly sensitive for pre-surgical localization of epileptogenic foci in patients with refractory epilepsy with inconclusive EEG and MRI. Inter-ictal FDG-PET has similar sensitivity to ictal SPECT for pre-surgical localization of epileptic foci in patients with non-contributory EEG and normal MR or MR findings discordant with the EEG findings. In 117 patients who underwent surgery for refractory extratemporal epilepsy, inter-ictal PET and ictal SPECT correctly localised the lesions in 77.7%, and 70.3% of the patients, respectively (Hwang *et al.* (2001).

2.3 Role of ^{18}F-FDG-PET/CT

Functional neuroimaging like ^{18}F-FDG-PET scanning can provide assessment of physiological and pathophysiological processes by measurement of molecular and biochemical changes that occur before they are visible on CT and MRI. PET/CT does

have some disadvantages including radiation exposure (comparable to CT alone), limited availability with possibly sedation requirement in some children (Kim *et al.,* 2010). FDG PET provides a helpful diagnostic result in determining patient's suitability to surgery especially if the children have normal or inconclusive MRI, bilateral lesions on MRI or in a setting where discordant focus between scalp EEG and MRI findings (Patil *et al.,* 2007). Nevertheless, various factors must be considered in managing intractable epilepsy children as not all of them fulfilled the criteria for surgical intervention (Rossi, 1995).

^{18}F –FDG PET/CT is one of developing nuclear medicine imaging which made possible by the unique fate of positrons from the decay of ^{18}F. ^{18}F is produced by cyclotron use widely in many PET centres as it does not require on site cyclotron due to its relatively long half-life (Le, 2006; Kim *et al.,*2010; Ziessman *et al.,* 2013). There are various numbers of radioactive tracers for PET to analyse the brain functions such as blood flow, glucose metabolism, protein synthesis, and neurotransmission. The most commonly used radiotracers for evaluation of brain glucose metabolism in the localization of epilepsy foci in current clinical practice is ^{18}F-FDG (Le, 2006; Kim *et al.,*2010).

^{18}F-FDG is transported into the cell similar to glucose allowing accurate assessment of regional cerebral glucose metabolism. It is able to cross the blood brain barrier to enter the neuron using glucose transporter systems and transformed into ^{18}F-FDG-6-phosphate. However, unlike glucose, FDG-6-phosphate remains unmetabolised after being trapped and accumulates in the cell at a speed proportional to glucose need. The metabolism of the cell is directly proportional to the intracellular concentration of ^{18}F-FDG-6-phosphate. In epilepsy, areas of possible epileptic origins will have reduce glucose metabolism hence showing reduced tracer uptake or better known as hypometabolic regions during interictal state (Le, 2006; Ziessman *et al.,* 2013).

^{18}F-FDG-PET/CT used in interictal state in comparison with ictal state due to its long uptake period approximately 40-60 minutes. Thus it is usually can be done in outpatient setting without the need to stop AED. The pathophysiology of regional hypometabolism in interictal FDG-PET is uncertain. A number of hypotheses have been advocated, including neuronal cell loss, neuronal inhibition, and diaschisis associated with hippocampal neuronal loss. Nevertheless, contradictory evidences exist such as temporal hypometabolism without neuronal loss or gliosis, and the poor correlation between metabolic change in the temporal lobe and hippocampal cell count. An inhibitory process and reduction in synaptic density also could be considered as other factors influencing interictal hypometabolism. It has been recommended that this secondary inhibition or neuronal loss in the area surrounding the epileptic zone may give rise to bigger and greater hypometabolism in FDG-PET/CT and hypoperfusion in SPECT compared to affected region seen on EEG or pathologic correlate (Kim *et al.,* 2010).

Clinical evaluation of ^{18}F-FDG-PET/CT is performed by visual inspection of the images by the expert in nuclear medicine imaging. The slices parallel to the frontocerebellar region are view from axial, coronal and sagittal axes with preferable polychromic color scale (Setoain, 2014).

Hypometabolism is considered focal when it is involved a single lobe or it involved contiguous regions in two adjacent lobes (Rathore *et al.,* 2014). Hypometabolism of the ipsilateral temporal lobe with or without less severe hypometabolism in the extratemporal structures such as frontal, parietal and contralateral temporal lobes are the usual pattern that can be observed in epilepsy patients. The degree of hypometabolism is greater than the size of the structural lesions if the lesion is related to epilepsy (Kim *et al.,* 2010).

Interictal PET is a very sensitive technique for lateralization and general localisation of seizure focus, however in a majority of the case it does not able to differentiate mesial from lateral temporal lobe epilepsy (TLE) due to extension of glucose hypometabolism in the mesial temporal to the lateral aspect of abnormal temporal lobe, hence surgical margin cannot be precisely defined (Sarikaya, 2014). This concept applies in all regions in the brain where FDG hypometabolism is not only limited to localizing the epileptogenic foci, but it is usually more widespread and beyond the true region of epileptogenic foci. Diaschisis or contralateral cerebellar hypometabolism can be seen in most of frontal or parietal lobes epilepsy (Kumar & Chugani, 2013). It is non-specific condition where there is functional disruption of reduced blood flow in cerebellum remote from contralateral cortical lesions due to neural activation (Ito *et al.,* 2002). ^{18}F-FDG-PET/CT images are reliable in lateralising temporal lobe epilepsy (TLE) in patients without a discrete neocortical mass lesion, with reported sensitivities of 60%–90% and few falsely lateralised cases (O'brien *et al.*, 2008).

2.4 Comparison of ^{18}F-FDG PET/CT with MRI

MRI plays a pivotal role in pre-surgical evaluation of patients for depicting gross structural lesions in the brain due to high resolution and multiplanar imaging technique. Anatomical definition of smaller lesions is possible with better definition of the larger destructive lesions. T1-weighted images allow better gray/white differentiation, T2-weighted images allow better visualization of subtle glial changes and edema especially in coronal views and FLAIR images offer improved contrast of cerebrospinal fluid and lesions (Keene & Ventureyra, 2000).

Carne *et al.* (2004) in their observation of previously 'normal' MRI finding, reexamination using modern imaging with high resolution using 3T MRI machine may have revealed subtle lesions, with likely seizure recurrence if unresected lesions remained. Detection of lesions on targeted high resolution 3T volumetric sequences and FLAIR studies is a common basis for reclassification of scans referred to their institution as 'normal'.

Few studies have shown MRI has high sensitivity in localisation of seizure foci. MRI shows structural abnormalities in 78 out of 120 subjects with most lesions detected was hippocampal sclerosis (Lefkopoulos, 2005). In extratemporal lesions, MRI showed a concordance rate of 84.2% with localization of the lesion in all concordant cases 84.2% (Kim *et al.,* 2009). Hwang *et al.* (2001) found lower detection rate of MRI as compared to FDG PET. The overall correct localization rate of the epileptogenic foci, including both neocortical temporal and extratemporal origins with MRI is only 59.8% as compared to FDG PET 77.7%. Nevertheless, detection of abnormalities by MRI was associated with good outcomes in this study. This result indicates that focal abnormalities, such as tumors, are well revealed by MRI and can be completely excised. Surgical outcomes associated with focal abnormalities will be better than those associated with diffuse or multifocal abnormalities, such as neuronal migration disorder or gliosis which has tendency to show subtle, diffuse, or multifocal lesions that is relatively insensitive to MRI. Majority of the patients with normal MRI findings in their study had neuronal migration disorder, although more than a half these patients had abnormal PET findings. All these findings suggest the role of PET as complementary tools to MRI in cases with normal MRI findings (Hwang *et al.,* 2001).

The normal MRI findings is a consistently proposed predictor of epilepsy surgical failure, because it represents a significant difficulties in achieving an accurate

preoperative localization of the epileptogenic focus, and indeed has been linked to poorer seizure outcomes following resective epilepsy surgery (Jeha *et al.*,2007). In a patient with normal MRI, planning for surgery is challenging as presence of frequently large epileptogenic zones due to widespread type I cortical dysplasia that does not direct the origin of seizure foci (Krsek *et al.*, 2008).

Interictal ^{18}F-FDG-PET/CT produces potentially quantifiable data with a superior spatial resolution to SPECT but less than that of MRI. Interictal FDG-PET/CT is more sensitive than MRI in localizing epileptogenic focus in both temporal and extra-temporal epilepsy (Kim *et al.,* 2010). ^{18}F-FDG-PET/CT images are reliable in lateralising TLE in patients without discrete neocortical mass lesion, with reported sensitivities of 60-90% and few falsely lateralized cases (O'Brien *et al.,* 2008).

Study by Uijl *et al.* (2007) showed ^{18}F-FDG-PET/CT has significant role when MRI and video EEG monitoring failed to localise epileptogenic zone. PET/CT findings have influenced the clinical decision making of approximately 71% of study population and 17% of these subjects were eligible for surgical intervention. In one retrospective study using a questionnaire to the managing clinicians on influence of FDG PET in patient management, it demonstrated that in patients who are suitable for surgery, the management is changed in 58% of patients with major changed in 39% (Ollenberger *et al.* 2005).

2.5 Factors associated with FDG hypometabolism

Not many studies have looked into different clinical factors that have influence on glucose metabolism in PET. Clinical factors can be classified into patient factor like age of onset and gender; disease factors like type of seizures, duration of epilepsy, frequency

of seizure attack, history of febrile convulsion and presence of developmental delay or autism as well as medication factor such as number of AEDs. A study shows significant relation between longer duration of seizure with focal hypometabolism in the temporal lobe with mean epilepsy duration is 20 ± 10 years. Their study proves the concept that hypometabolism not inevitably present initially but may develop over period of more than 10 years. However, their study did not find a significant association in history of febrile seizure or presence of generalised tonic-clonic seizure in mesial temporal hypometabolism (Theodore *et al.,* 2004)

Epilepsy duration was inversely proportional with FDG hypometabolism in the inferior temporal gyrus, hippocampus, and parahippocampal gyrus of the epileptogenic temporal cortex ($p < 0.05$). Age at seizure onset did not affect the correlation between epilepsy duration and glucose metabolism except in the inferior temporal gyrus ($p < 0.05$) (Akman *et al.,* 2010). Wong *et al.* (2010) proved that the side of the surgery, history of febrile seizure, age of seizure onset, duration of epilepsy prior to FDG PET, and the age at which the FDG-PET scan was performed not significantly affect the extent of focal and unilateral FDG hypometabolism. However, the presence of generalised tonic clonic seizure was significantly associated with the extent of unilateral hypometabolism ($p < 0.005$).

Tuberous sclerosis is one of common etiology in children with refractory seizure. Several studies proven the location of tubers in temporal lobe as well as local epileptic origins at these regions have association with autism among the affected patients. A study of 31 children with tuberous sclerosis showed 17 of them has autistic spectrum disorders with probable or possible temporal EEG focus and several had a history of infantile spasms (Bolton *et al.,* 2002)

Mohamed *et al.* (2011) in the study of 16 childrens who underwent temporoparietooccipital disconnection surgery found all of the children with refractory epilepsy have significant developmental delay. Malformations of cortical developments such as tuberous sclerosis, focal cortical dysplasia and hemimegalencephaly are strongly associated with refractory epilepsy and developmental delay (Guerrini, 2005; Leventer *et al.,* 2008). Few factors such as history of febrile seizures and head injury, epilepsy duration, frequency of seizure with impaired cognition in the last 3 months, presence of secondarily generalized tonic–clonic (GTC) seizure, automatism side, and presence of postictal confusion have failed to demonstrate a significant association in the assessment of the FDG PET temporal lobe hypometabolism with involvement of contralateral side causing bilateral temporal hypometabolism (Tepmongkol *et al.,* 2013).

CHAPTER 3

OBJECTIVES

3.1 Justification of the study

In Malaysia, ^{18}F-FDG PET/CT is being used in refractory epilepsy in children as a presurgical evaluation. ^{18}F-FDG PET/CT will detect an areas or regions with focal hypometabolism which can guide the physician's decision making in the management of refractory epilepsy patient. It is particularly important in patient who has discordance scalp EEG and MRI finding, no focal lesion seen on MRI or unclear margin and multiple lesions seen on MRI as these group of patients often giving a management challenge to physicians. To my knowledge this is the first study in Malaysia to look at the added value of ^{18}F-FDG-PET/CT in the presurgical evaluation of refractory paediatric epilepsy patient. Data review of the patients correlating with their clinical history and blinded review of PET/CT images by nuclear medicine physicians using visual assessment was done. Findings of FDG PET/CT were subsequently compared with MRI and EEG results. Several clinical factors which related to patient, disease and treatment were assessed in their association with FDG hypometabolisms.

3.2 Benefits of the study

1. To create local data of refractory epilepsy in paediatric population in Malaysia

2. To guide clinicians for future improvement of the management of refractory epilepsy in children who undergo presurgical evaluation.

3.3 General objective

To assess the role of ^{18}F-FDG-PET/CT as a valuable functional neuroimaging in pre-surgical evaluation of refractory paediatric epilepsy.

3.4 Specific objectives

1. To assess detection rate of ^{18}F-FDG-PET/CT in detecting foci hypometabolism in refractory paediatric epilepsy patients with normal or inconclusive MRI.

2. To assess the use of ^{18}F-FDG-PET/CT when there is a discordant MRI and EEG finding or when the findings of MRI were inconclusive.

3. To identify the significant associated clinical factors with the presence of foci hypometabolism in ^{18}F-FDG-PET/CT.

3.5 Research hypothesis

1. ^{18}F-FDG-PET/CT has high percentage in detecting foci hypometabolism in normal or inconclusive MRI findings in refractory paediatric epilepsy.
2. ^{18}F-FDG-PET/CT is helpful in determining the localization of epileptic foci in refractory paediatric epilepsy with discordant MRI and EEG findings or inconclusive MRI.
3. Various clinical factors are significantly associated with foci hypometabolism in ^{18}F-FDG-PET/CT.