ROLE OF ^{18}F-FDG PET SCAN IN LOCALIZATION OF NON-LESIONAL EPILEPTOGENIC ZONE

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ABSTRACT

OBJECTIVES: To investigate the role of ^{18}F-fluorodeoxyglucose positron-emission tomography (FDG-PET) in localizing epileptogenic focus of patients with refractory focal epilepsy and normal brain magnetic resonance imaging (MRI). **MATERIAL AND METHODS:** In this cross-sectional study, all patients were evaluated clinically and with in-hospital video electroencephalography monitoring (VEM) to localize epileptogenic focus. All patients had unremarkable brain MRI. FDG-PET of brain performed to localize the epileptogenic focus. We used expert visual analysis method in addition to statistical parametric mapping (SPM) and asymmetry index to evaluate brain cortex metabolic activity. We stratified patients with regard to clinical epileptogenic focus as localized in temporal lobe, frontal lobe or partially localized. Finally, clinical and VEM data were compared with FDG-PET results to determine congruence between clinical/VEM data and FDG-PET. **RESULTS:** Among patients with temporal lobe epileptogenic focus, 62.5% exact congruency with PET results was documented ($p<0.001$), contrary to 29.7% incongruence. Patients with frontal lobe epileptogenic focus had only 6.6% exact congruency ($p>0.05$) and 13.3% partial congruency was documented. Finally, among patients with partially localized seizure focus in one hemisphere, only 6.6% exact congruency ($p>0.05$) and 53.3% incongruence was demonstrated. **CONCLUSION:** Overall PET results in frontal lobe or partially localized seizure patients were not promising in our study. Although majority of temporal lobe seizure patients demonstrated exactly congruent PET results, these results may be further enhanced by more precise localization of seizure focus with clinical evaluations and VEM, in addition to utilizing more advanced PET imaging software to better quantify and compare PET image findings.
Keywords: Epilepsy, Seizure focus, FDG-PET, VEM

Introduction

Epilepsy is a chronic neurologic disorder that affects approximately 1% of the population in the world with an incidence rate of 70 per 100,000 persons per year.[1] About one third of patients with focal epilepsy do not respond to pharmacotherapy.[2] In these patients, epilepsy surgery is a potentially curative option.[3] Video-EEG monitoring (VEM) and identification of structural lesions by imaging modalities are mainstays

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of pre-surgical evaluation.[4] Magnetic resonance imaging (MRI) is a powerful tool to identify the lesions causing epilepsy but still fails to reveal any apparent abnormality in approximately 20% of the patients with medically refractory epilepsy.[5] In these cases, which have a worse prognosis for seizure-free outcome, the role of functional imaging modalities of cerebral metabolism such as ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) scan is more evident.[6,7] Decreased glucose metabolism in interictal FDG-PET scans may be helpful in localization of epileptogenic focus and also reduce the need for invasive EEG monitoring.[8,9]

FDG-PET has a sensitivity of 70-85% in patients with temporal lobe epilepsy (TLE) with the most useful results in those with normal brain MRI. However, the diagnostic value in extra-temporal lobe epilepsy (ETLE) is significantly lower and limited to 30-60%.[8,10] The concordance of data extracted from MRI, FDG-PET and VEM has a significant effect on precise localization of epilepsy and might improve post-surgical outcome.[9,11]

Most of existing studies investigated the role of FDG-PET in a mixed population of patients with and without visible lesions in MRI and some of them used both scalp and invasive EEG monitoring. In this study which is the first experience nationwide, we determined the degree of congruency between clinical and scalp EEG monitoring data with FDG-PET in patients with refractory focal epilepsy and normal brain MRI to understand usefulness of FDG-PET in pre-surgical localization of epileptogenic zone. We also specified the role of this concordance to obviate the need for invasive EEG monitoring.

Material and Methods

This is a cross-sectional study aiming to evaluate patients suffering from refractory partial epilepsy and normal brain MRI, referred by two expert neurologists to localize the seizure focus by means of FDG-PET scan. The institutional review board (IRB) approved this study. All participating patients signed an informed consent, allowing use of their medical information in this research.

Patient selection:

In this study we enrolled all patients referred to our PET scan department from March 2017 to March 2019 to confirm the localization of epileptogenic focus by means of FDG-PET scan meeting the following inclusion criteria: suffering from focal drug-resistant epilepsy, having unremarkable brain MRI interpreted with an expert neuroradiologist and having detailed clinical and in-hospital EEG monitoring to localize the epileptogenic focus. Drug-resistant epilepsy was defined as failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.[2]

Clinical (semiology) evaluation:

All patients were clinically evaluated in an epilepsy center supervised by two expert neurologists with epilepsy fellowship training experience. Comprehensive history of all patients were recorded precisely including: brief history of epilepsy, seizure type, evolution, frequency, age of onset, risk factors, social history, family history, past and current anti-epileptic medications, positive findings on physical and neurological examination, labs and anti-epileptic drug levels and the previous investigations.

Electroencephalography evaluation:

All patients underwent prolonged scalp EEG monitoring using 64-channel Nihon Kohden system. Electrodes arranged according to the International 10 20 systems with additional temporal electrodes (F9, F10, T9, T10, T1 and T2). The setting was arranged at 200 Hz sampling rate, 0.1 second time constant and 60 Hz notch filter. During EEG monitoring in the inter-ictal phase; frequency of background activity and spikes characteristics were recorded. In the ictal phase all seizure activities including type, number, duration, laterality and spread were also recorded. Then an epilepsy report including clinical classification information and suggested irritative and epileptogenic zones according to semiology and EEG results were generated.

MRI imaging:

All patients referred for a dedicated brain MRI in the epilepsy center (Siemens, 1.5 Tesla, magnetom essenza, syngo SPACE) in following sequences: Axial

T1, T2; Coronal T1IR, T2; FLAIR; Sagital T2 and 3D MPRAGE brain MRI without contrast media. All brain MRI images were interpreted by an expert neuro-radiologist and unremarkable brain MRI cases were referred to our FDG-PET department for further evaluation.

FDG-PET imaging:

The selected patients for FDG-PET underwent EEG monitoring started at least 2 hours before FDG injection which continued at least for 20 minutes after FDG injection to detect any possible unrecognized seizure activity. If seizure activity happens during FDG uptake time; it can cause dramatic effect on the image interpretation, resulting in false seizure focus lateralization.[12] All patients with suspicious EEG activity suggestive for ictal activity during uptake time were rescheduled to have repeat study.

All patients were injected intravenous FDG with the dose of 4.6 MBq/Kg according to SNMMI (society of nuclear medicine and molecular imaging) guidelines. Before FDG injection, blood glucose was measured for all patients to ensure it is in desirable range (80-150 mg/dL). After 60 minutes uptake time in a dimly lit room with minimum visual and auditory stimulants, the patients would undertake dedicated FDG-PET brain imaging under discovery 690 VCT (GE Healthcare, Milwaukee, USA), equipped with 64-slice CT (Light Speed VCT) machine from vertex to skull base for 20 minutes in single consistent head position. Following CT acquisition, the emission data were obtained in 20 minutes in one bed position (from vertex to skull base) that reconstructed with modified ordered-subset expectation maximization (OSEM), point-spread-function (PSF) and time of flight (TOF) protocol.

The attenuation corrected brain PET images were evaluated on an GE (General Electric) advantage work station (ADW 4.5) by two expert nuclear medicine physicians and radiologists simultaneously, primarily unaware of seizure focus localization results based on prior semiology and EEG evaluations.

For quantitative analysis, we used CortexIDfi software (developed by GE healthcare) installed on ADW 4.5 station. Cortex ID software can generate three dimensional stereotactic surface projections (3DSSP) to evaluate the overall brain cortex metabolic activity. Then the statistical parametric mapping (SPM) is generated by software by comparison of local peak metabolic activity values at standardized anatomical locations with the corresponding reference normal peak activity in age stratified control subjects (Fig. 1,2).

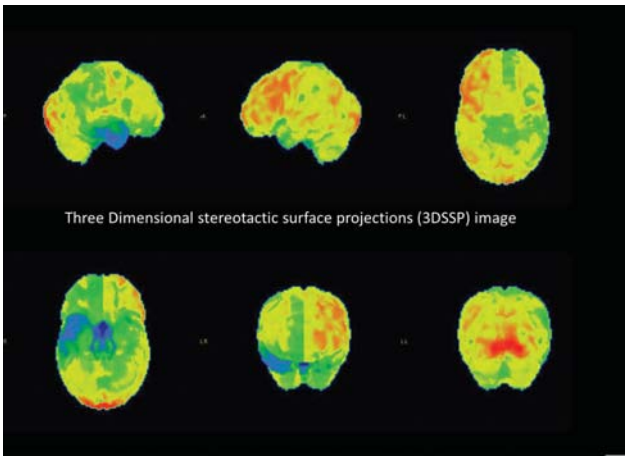

Figure 1: Three Dimensional Stereotactic Surface Projection (3DSSP) image, demonstrating sever decreased right temporal lobe metabolic activity compared to remainder of brain cortex.

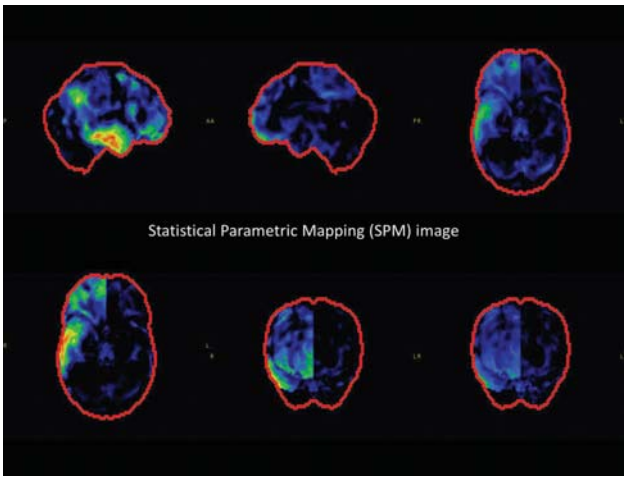

Figure 2: Statistical parametric mapping (SPM) image in the same patient demonstrates statistically significant decreased metabolic activity in the right temporal lobe comparing to the age-matched control group.

The statistical differences in standardized anatomical locations were expressed as Z-scores compared to reference point which was selected to be the Pons in our patients as it is less affected by seizure neuronal pathways in the seizure patients, contrary to other reference points including the cerebellum and thalamus as their metabolic activity might be affected during seizure activities for example by neuronal diaschisis.

We also used expert visual analysis method to

compare the metabolic activity in the suspected regions with normal contralateral side. At present there is little evidence to suggest that quantitative approaches such as statistical parametric mapping (SPM) are more accurate for localization of seizure foci than expert visual analysis.[13-15]

We used step 10 color scale as our preferred method to compare areas with decreased metabolic activity, as each change in the color scale is equivalent with 10% change in brain cortex metabolic activity. For patients with temporal lobe epilepsy and bilateral temporal hypometabolism shown on PET images; we additionally calculated the asymmetry index based on maximum standardized uptake values (SUVmax) of the temporal sub-lobar regions of interest (ROI) calculated according to the following formula: (left - right) / [(left + right) / 2] 100%. An asymmetry index of >10% will be considered significant[16,17] (Fig. 3).

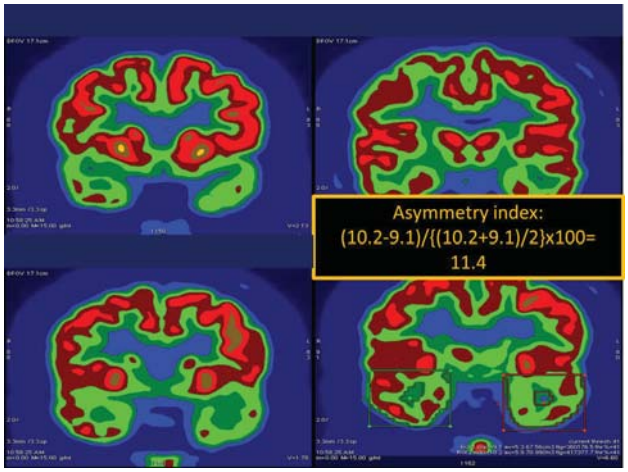

Figure 3: Step-10 color scale FDG-PET brain image demonstrating visually subtle difference between temporal lobes. However, calculation of SUVmax values in each lobe and using asymmetry index, demonstrated more than 10% difference between right and left temporal lobe (less metabolic activity on the left lobe), confirming the epileptogenic focus.

Image interpretation and statistical analysis:

Exact congruency was defined as anatomically matching results between all three diagnostic methods including: Clinical evaluation, VEM data and FDG-PET results. Partial congruency was defined as matching FDG-PET results with either clinical or VEM seizure localization. Incongruence was defined as no anatomical matching between any of the three mentioned methods.

The prevalence of patients in temporal lobe seizure, frontal lobe seizure and partially localized seizure groups was determined with regard to congruency between the FDG-PET results and clinical/VEM data. To consider statistically significant results, the p-value of <0.05 was chosen.

We also performed Cohen's Kappa-Coefficient (k) test to measure inter-rater agreement between our qualitative items including seizure focus localization and congruency with FDG-PET results.

Results

In this study we included 124 patients (64 males and 60 females) with mean age of 28.5 years, ranging between 5 and 62 years.

64 patients had their seizure focus localized in temporal lobe by means of clinical and VEM data in which 40 patients demonstrated exactly congruent PET results (62.5%) ($p<0.001$). 5 patients demonstrated partially congruent PET results (7.8%) and 19 patients had totally incongruent PET findings (29.7%).

30 patients had their seizure focus localized in frontal lobe by means of clinical and VEM data in which 2 patients demonstrated exactly congruent PET results (6.7%) ($p>0.05$). 4 patients demonstrated partially congruent PET results (13.3%) and 24 patients had totally incongruent PET findings (80%).

30 patients had their seizure focus only partially localized by means of clinical and VEM data in which 30 patients demonstrated exactly congruent PET results (6.7%) ($p>0.05$). 12 patients demonstrated partially congruent PET results (40%) and 16 patients had totally incongruent PET findings (53.3%).

Majority of exactly congruent PET results (91%) had their seizure focus localized in temporal lobe. Among partially congruent cases; 5 patients (23.8%) had their seizure focus localized in temporal lobe, 4 patients (19%) in frontal lobe and 12 other patients (57.2%) have only been partially localized. Among incongruent cases; 19 patients (32.2%) had their seizure focus localized in temporal lobe, 24 patients (40.7%) in frontal lobe and 16 other patients (27.1%) have only been partially localized (Tab. 1).

Evaluation of our PET scans demonstrated 40 negative (no localized focus with decreased metabolic activity) brain PET scans, in which 14 patients (35%) had their seizure focus clinically localized in temporal

Seizure focus / Congruency	Temporal lobe	Frontal lobe	Partially localized	Total
Congruent	40	2	2	44
Partially congruent	5	4	12	21
Incongruent	19	24	16	59
Total	64	30	30	124

Table 1: Degree of congruency between clinical seizures foci and brain PET results

lobe. Another 14 patients (35%) had their seizure focus localized clinically in frontal lobe and 12 patients (30%) have only been partially localized on clinical and EEG evaluation.

(Tab. 2) summarizes our findings to measure inter-rater agreement to calculate Cohen's Kappa-Coefficient (k). The inter-rater agreement for seizure focus localization in temporal lobe was 0.49 (k=0.49), consistent with moderate agreement. However, the inter-rater agreement for overall seizure focus localization was 0.35 (k=0.35), consistent with fair agreement.

FDG-PET Seizure focus localization	Clinical/VEM seizure focus localization			
	Temporal	Frontal	Partially localized	Total
Temporal	40	4	6	50
Frontal	1	2	22	25
Partially localized	23	24	2	49
Total	64	30	30	124

Table 2: Inter-rater agreement for seizure focus localization

Discussion

FDG-PET is a useful tool to evaluate patients with refractory TLE. However, utility of FDG-PET scan in localization of extra-temporal epileptogenic focus is much more limited.[8,10,18]

FDG-PET can provide additional information about the epileptic focus in up to two thirds of cases, affecting surgical decision making in up to 50% 70% of cases and sometimes changing initial decisions based on MRI or VEM.[19,20] FDG-PET has been found to be most useful when MRI findings are negative or when ictal EEG is discordant with MRI or seizure semiology.[20]

Patients with frontal lobe epilepsy (FLE) generally have a less favorable post-surgical outcome particularly in the presence of non-lesional MRI and lack of intracranial EEG monitoring.[21-24] Scalp EEG monitoring could be misleading and non-localizing due to short duration of seizures which are usually contaminated with excessive artifacts and presence of secondary bilateral synchrony.[22,25,26] FDG-PET is helpful in localization of epileptogenic zone in these patients, although the sensitivity significantly reduces in non-lesional patients.[27-29] Our results for localization of epileptogenic zone in patients with FLE were unpromising and incongruent which in part could be explained by absence of structural lesion in MRI and also poor EEG localization due to lack of intracranial EEG monitoring.

Despite the common favorable surgical outcome in TLE, the rate of patients with postoperative seizure freedom is lower in non-lesional patients.[30], but concordant FGD-PET hypometabolism in patients with non-lesional TLE has a positive predictive value for favorable outcome.[31,32] Dramatically different from FLE, we demonstrated 62.5% exact congruency between semiology/VEM results and FDG-PET in patients with TLE which is comparable, but still below the results from other investigators. 76-90% sensitivity has been reported by different studies for detection of the epileptogenic zone by FDG-PET in TLE[31,33] and it has been proven that FDG-PET can be helpful to identify the epileptogenic temporal lobe focus in almost half of patients with non-contributory EEG.[34] One of the reasons that might contribute to our lower performance comparing to the literature is significant number of partially localized epileptogenic foci due to lack of intracranial EEG monitoring. Among our 124 patients; the semiology and EEG monitoring was not able to exactly determine the epileptic focus in 30 cases (24.2%). We assumed that when the epileptic focus is not precisely localized clinically, probably the FDG-PET would be less contributory to confirm the epileptogenic focus.

Moreover, temporal lobe inter-ictal hypometabolic regions often extend beyond the presumed epileptogenic zone.[31] Patients may show hypometabolism in the ipsilateral parietal and frontal cortex, thalamus and even occasionally in the contralateral temporal lobe[35] (diaschisis pattern). This pattern may represent the more extended epileptic network involved in seizure propagation[31] and explain the partial incongruent FDG-PET/VEM findings in about 17% of our patients.

Another contributing reason might be unavailability of most advanced and sophisticated brain PET analysis software s such as MIMneurofi (developed by MIM software Inc. Cleveland, OH), with no official agent in our country. Utilizing MIMneurofi software, for example; comparing to CortexIDfi, enables the diagnostician to perform more accurate quantification of the metabolic activity in the brain sub-regions and probably generates more reliable statistical parametric mappings (SPM).

Overall, radionuclide imaging may be particularly useful if brain MRI imaging findings are negative or show multifocal lesions of which only one or two are suspected to be epileptogenic and if VEM changes are equivocal or discordant with the structural imaging.

Conclusion

FDG-PET scan is very helpful in epileptogenic focus localization when the epileptogenic zone is in temporal lobe. However, the sensitivity is significantly lower in localization of extra-temporal epileptogenic foci.

The more precise is the localization of epileptogenic focus on clinical evaluation and VEM; the more helpful would be the subsequent FDG-PET scan to confirm the semiology/VEM findings. Our results need to be further validated in larger studies.

Compliance with Ethical Standards:

Funding: The authors certify that they have no funding resource for this research.

Conflict of interest: The authors declare that they have no conflict of interest for this research.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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