

Navigating the Brain: The Role of 18F-FDG PET/CT in Pinpointing Epileptic Foci

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Abstract

Background: Epilepsy is a chronic neurological condition marked by recurring seizures. The 18F-fluoro-2-deoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) technique is thought to be useful for determining the location of epilepsy. However, its ability to detect the epileptic zone in patients with drug-resistant epilepsy (DRE) remains unclear. Therefore, we aimed to determine the role of 18F-FDG PET/CT in localization of temporal and extratemporal epilepsies in patients with refractory epilepsy.

Methods: This is a cross-sectional study examining patients with refractory epilepsy who were admitted to Masih Daneshvari Hospital, Iran. This study includes patients with refractory epilepsy who had normal brain magnetic resonance imaging (MRI) results. The seizure focus was indicated by two professional neurologists using a video-electroencephalography monitoring (VEM). All patients received an intravenous injection of FDG at a dosage of 4.6 MBq/kg. The patient's records and FDG PET/CT results were then checked, and if they were congruent, the patient would undergo surgery and resection of the epileptic region. The data were reported using descriptive statistics. We also used Cohen's kappa coefficient (*k*) test to assess interrater agreement between temporal lobe localization and congruency with FDG-PET data.

Results: Our investigation revealed that 65.60% of seizures occurred in temporal lobe, with 67.96% exhibiting congruent PET results. Furthermore, 25.4% had a focus in frontal lobe, while only 12.5% showed congruent PET results. Temporal lobe was the focus of the majority (92.1%) of congruent PET data, as well as 36.3% of partially congruent PET data and 42.3% of incongruent PET data. PET scans revealed that 28.1% were negative, with 47.7% clinically focused in temporal lobe, 38.6% in the frontal lobe, and 13.6% only partially localized. In addition, the interrater agreement for seizure focus localization in temporal lobe was 0.71, indicating substantial agreement.

Conclusion: FDG PET/CT was shown to be an acceptable technique for identifying DRE, namely temporal lobe epilepsy. The gold standard methods can provide more accurate epilepsy zone localization, resulting in better FDG PET/CT congruency.

Keywords: 4-Fluoro-4-Deoxyglucose, Positron Emission Tomography Computed Tomography, Epilepsy, Seizures

Abbreviations

- **18F-FDG PET/CT:** 18f-Fluoro-2-Deoxyglucose Positron Emission Tomography/Computed Tomography
- **DRE:** Drug-Resistant Epilepsy
- **MRI:** Magnetic Resonance Imaging
- **VEM:** Video-Electroencephalography Monitoring
- **k:** Kappa Coefficient Test
- **EEG:** Electroencephalography
- **MR:** Magnetic Resonance

1. Introduction

Epilepsy is a chronic neurological disorder characterized

by recurring seizures that affects approximately 50 million people worldwide. DRE manifests in approximately 20-30% of individuals diagnosed with focal epilepsy. This indicates that despite undergoing treatment with a minimum of two antiseizure medications, patients persist in experiencing seizures [1]. The management of these patients poses challenges due to an incomplete understanding of its underlying mechanism, as well as the variable occurrence of pharmacoresistance in certain individuals. Generally, respective surgery is associated with the most favorable outcomes in terms of seizure control in these patients [2]. In the initial phase of evaluating epilepsy surgery candidacy,

various tests are performed to identify the specific brain region responsible for seizures. These include medical history review, physical examination, prolonged scalp VEM, brain MRI, and neuropsychological testing. If a clear lesion is found and the video-EEG results align with MRI findings, surgery may be considered [3].

Recent advancements in PET imaging, particularly PET/CT, have improved image quality and resolution, especially in patients with epilepsy [4-6]. Among the various techniques used in routine clinical practice, imaging brain glucose metabolism with ^{18}F -FDG PET/CT is the most prevalent [7]. This imaging technique is widely recognized as a noninvasive method for monitoring changes in cerebral glucose metabolism (glucose hypometabolism) within epileptogenic foci. The underlying mechanism of this imaging modality involves the transportation of ^{18}F -FDG from circulation into brain cells via glucose transporters, with its transfer to brain tissue directly linked to increased glucose consumption [8]. By employing different FDG-PET tracers capable of assessing brain oxygen metabolism, cerebral blood flow, and serotonin concentration, their benefits in determining the seizure focus area are maximized [9]. Since the precise localization of the epileptogenic zone remains a major challenge, this method has been employed to aid in localizing seizure foci [7]. Research indicates that ^{18}F -FDG PET plays

a crucial role in preoperative assessment, offering lateralizing or localizing information in 60–90% of individuals with temporal lobe epilepsy [10,11]. To some extent, the reason for this difference lies in different techniques used for image analysis. The physiological basis of lesion hypometabolism is indeterminate and may be due to reduced synaptic activity, anatomical differences, or disruptions in the white matter pathway [11].

Although the ^{18}F -FDG PET/CT technique is considered useful for determining the location of epilepsy, its ability to detect the epileptic zone in patients with DRE remains unclear. Due to the importance of managing DRE appropriately and the shortage of evidence on the efficacy of ^{18}F -FDG PET/CT, we aimed to explore its role in localizing temporal and extratemporal epilepsies in refractory epileptic patients. We hypothesized that identifying the seizure focus in temporal lobe as a hypometabolic center could indicate a positive predictive factor for surgical treatment eligibility in DRE patients (Figure 1). If clinical and electroencephalographic findings align with FDG PET results and if the patient is a potential candidate for seizure-focus resection or ablative surgery, surgery is recommended. Additionally, it has been proposed that patients with a focal lesion on brain MRI may benefit from more extensive surgery if the hypometabolic area is larger than the observed lesion.

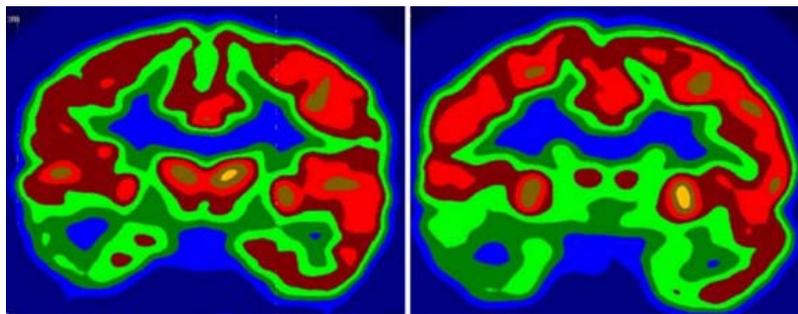


Figure 1: Color Scale Demonstrating Decreased Local Metabolic Activity in Right Temporal Lobe, Related to Epileptogenic Focus

2. Methods

2.1. Participants and Settings

This is a cross-sectional study aiming to evaluate patients suffering from refractory epilepsy referred to Masih Daneshvari Hospital, Iran. Patients with refractory epilepsy and normal brain MRI findings were enrolled in this study. Refractory epilepsy was defined as the persistence of seizures despite the use of two antiseizure medications, either singly or in combination. Normal brain MRI results were characterized by the absence of any anatomical or structural abnormalities.

2.2. Data Gathering

Data were obtained using a form containing demographic characteristics such as sex and age, as well as electroencephalography (EEG) data indicating the epileptogenic focus. Following initial physical and imaging examinations, patients were evaluated using FDG PET/CT. The collected images were examined using the visual scale approach to

identify hypometabolic zones that may indicate an epilepsy-producing zone. Seizure foci were identified using FDG-PET scans analyzed by two neurologists. Patients chosen for FDG-PET had EEG monitoring that began at least two hours before FDG injection and lasted at least 20 minutes afterward to detect any potential unidentified seizure activity. Any seizure activity occurring during the FDG uptake period could have a major impact on picture interpretation, perhaps resulting in incorrect seizure focus localization. Patients with suspicious EEG activity suggesting ictal activity during the uptake period were rescheduled for repeated tests [12].

All patients received intravenous FDG injections at 4.6 MBq/kg, in accordance with the Society of Nuclear Medicine and Molecular Imaging's standards. Before FDG injection, all patients' blood glucose levels were monitored to ensure that they were within the ideal range of 80-150 mg/dL. Following a 60-minute uptake period in a dimly lit

room with minimal visual and auditory stimuli, patients underwent dedicated FDG-PET brain imaging [GE Healthcare, Milwaukee, USA], which included a 64-slice CT machine that covered the area from the vertex to the skull base for 20 minutes in a single consistent head position. Subsequently, the patient's prior medical records were obtained with the findings derived from FDG PET/CT. In cases of appropriateness and consistency, surgical intervention involving resection of the epileptic foci was recommended for the patient. Exact congruence was defined by anatomically corresponding outcomes across all three diagnostic modalities, including clinical evaluation, VEM data, and FDG-PET results. Partial congruence was established when FDG-PET findings aligned either with clinical evaluation or VEM seizure localization. Incongruence was characterized by the absence of anatomical alignment among any of the aforementioned diagnostic methods.

The frequency rates of patients in groups experiencing temporal lobe seizures, frontal lobe seizures, and partially localized seizures were assessed based on the alignment between FDG-PET findings and clinical/VEM data congruency.

2.3. Ethical Considerations

This study was approved by the ethics committee of the Vice-Chancellor of Research at Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1400.230).

2.4. Statistical Analysis

The data were reported using descriptive statistics (mean, standard deviation, number, and percentage) in IBM SPSS Statistics for Windows, version 21. We also used Cohen's kappa coefficient (κ) test to assess interrater agreement between temporal lobe localization and congruency with FDG-PET results. The results were categorized as follows:

slight agreement=0.0-0.2; fair agreement=0.2-0.4; moderate agreement=0.4-0.6; substantial agreement=0.6-0.8; and almost perfect agreement=0.8-1.0.

3. Results

In this study, 157 patients (84 men and 73 women) with a mean age of 28.88 ± 11.31 years were evaluated. Among all patients, 76 (48.4%), 22 (14.01%), and 59 (37.57%) congruent, partially congruent, and incongruent PET results, respectively, were noted. Clinical and VEM data revealed that 103 (65.60%) patients had seizure foci located in temporal lobe, with 70 patients demonstrating exactly congruent PET results (67.96%). Clinical and VEM data revealed that forty patients (25.4%) had their seizure focus located in frontal lobe, with five patients demonstrating exactly congruent PET results (12.5%). In frontal lobe, FDG PET/CT revealed partial congruency and incongruence in 9 (22.5%) and 26 (65%) patients, respectively.

According to clinical and VEM data, the seizure focus of fourteen patients (8.9%) was only partially localized, with one patient demonstrating exactly congruent PET results (7.1%), five patients demonstrating partially congruent PET results (35.7%), and eight patients demonstrating incongruent PET findings (57.1%). The majority of exactly congruent PET results (92.1%) had a seizure focus located in temporal lobe. Among patients who demonstrated partial congruence, 8 individuals (36.3%) exhibited a seizure focus within temporal lobe, 9 individuals (40.9%) within frontal lobe, and 5 individuals (22.7%) whose seizures were only partially localized. Among the incongruent patients, 25 patients (42.3%) had seizures localized to temporal lobe, 26 patients (44.1%) had seizures localized to frontal lobe, and 8 patients (13.5%) had seizures only partially localized in temporal lobe (Table 1 and Figures 2 and 3).

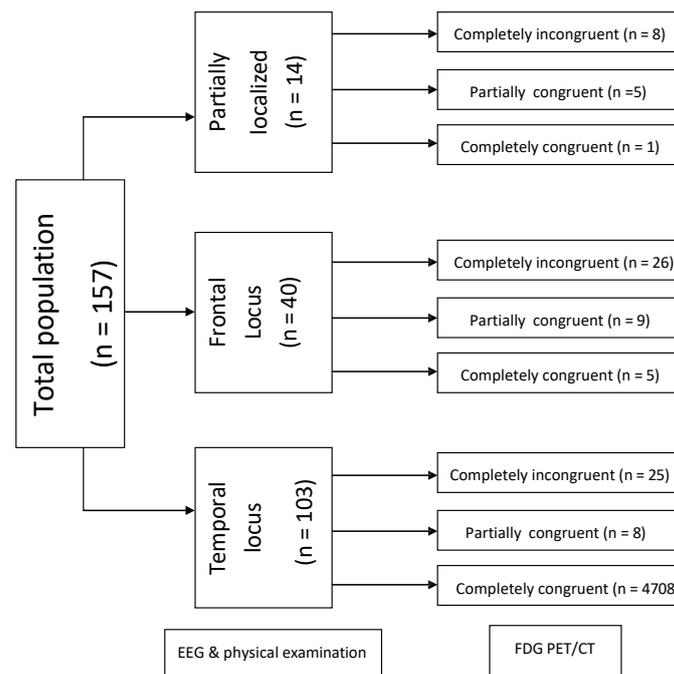


Figure 2: The Degree of Congruence of Eeg and Physical Examination with Fdg Pet/Ct

Congruency	Seizure focus			
	Temporal (number)	Frontal (number)	Partially localized (number)	Total (number)
Congruent (number)	70	5	1	76
Partially congruent (number)	8	9	5	22
Incongruent (PET neg. included) (number)	25	26	8	59
Total (number)	103	40	14	157

Table 1: Degree of Congruency Between Clinical Seizure Foci and Brain Pet Results

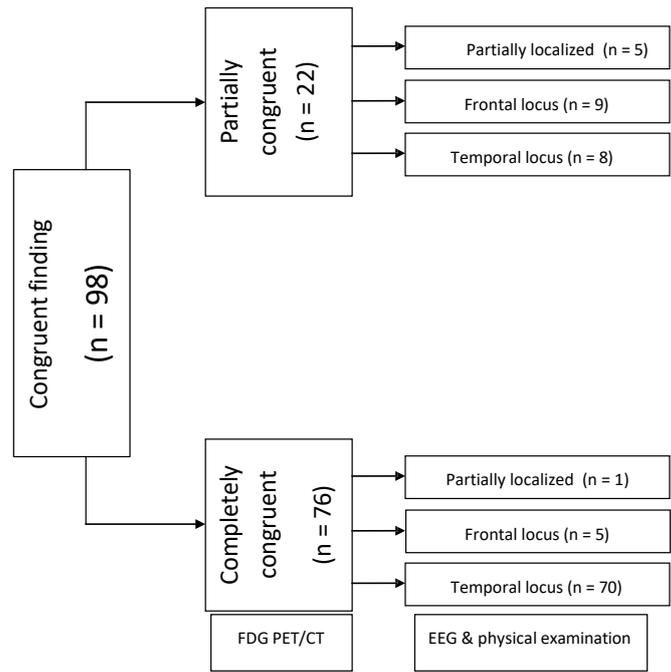


Figure 3: The Results of Eeg and Physical Examination Compared to Fdg Pet/Ct

Our PET scan analysis revealed 44 (28.1%) negative (no localized focus with decreased metabolic activity) brain PET scans, with 21 patients (47.7%) having a seizure focus clinically localized in temporal lobe. In another 17 patients

(38.6%), the seizure focus was clinically located in frontal lobe, whereas in 6 patients (13.6%), the seizure focus was only partially localized after clinical and EEG assessments (Table 2).

FDG-PET seizure focus localization	Clinical/VEM seizure focus localization			
	Temporal (number)	Frontal (number)	Partially localized (number)	Total
Temporal (number)	73	9	7	89
Frontal (number)	2	5	-	7
Partially localized(number)	7	9	1	17
Negative (number)	21	17	6	44
Total (number)	103	40	14	157

Table 2: Interrater Agreement for Seizure Focus Localization

According to these data, the interrater agreement for localizing seizure foci in temporal lobe was 0.71 (k=0.71), indicating substantial agreement.

4. Discussion

FDG-PET has emerged as a valuable tool for assessing patients with DRE. Its holistic approach, which involves the merging of metabolic insights with anatomical imaging, enhances the precision of identifying seizure foci, thus facilitating treatment strategies for individuals with refractory epilepsy. In our study, 76 (48.4%), 22 (14.01%), and 59 (37.57%) congruent, partially congruent, and incongruent PET results, respectively, were noted among all patients. We also observed that 65.60% of patients exhibited seizure foci in temporal lobe, with 67.96% showing congruent PET results. Conversely, 25.4% had foci in frontal lobe, yet only 12.5% displayed congruent PET results. Notably, the majority (92.1%) of congruent PET results were localized to temporal lobe, while 36.3% of partially congruent cases and 42.3% of incongruent cases also exhibited focus in temporal lobe. Analysis of PET scans revealed that 28.1% were negative; among these, 47.7% clinically exhibited focus in temporal lobe, 38.6% in frontal lobe, and 13.6% were only partially localized.

Upon diagnosing DRE, prompt consideration of epilepsy surgery is crucial, as delaying surgery could potentially diminish postoperative seizure-free rates [13]. Patients with MRI findings consistent with epilepsy demonstrate greater rates of postsurgical seizure-free status than those with normal MRI findings; however, a normal MRI should not prevent surgical evaluation [14]. Despite well-documented improvements in outcomes, there remains a significant 20-year delay, on average, before a typical patient with DRE is referred to an epilepsy surgery center [15]. Upon referral, the suitability for epilepsy surgery must be assessed, necessitating a comprehensive, multiparametric, and multimodal approach to precisely localize the epileptogenic focus. In addition to confirming the localization of epilepsy through testing, other factors, such as the disabling nature of seizures, the location of epilepsy relative to vital brain regions, and potential risks to cognition and memory from surgery, must also be taken into consideration [2].

FDG-PET is particularly valuable for patients who are MRI-negative or in instances where nonspecific abnormalities are present [16]. A decade ago, an 18F-FDG PET scan was performed for the majority of patients to highlight hypometabolic zones interconnected with the onset of seizures on scalp EEG [17]. In such cases, the identification of hypometabolism coinciding with electroclinical findings may justify proceeding to surgery without additional assessment. In other words, when MRI fails to detect a lesion, 18F-FDG PET may be beneficial for revealing hypometabolism in temporal lobe, which reinforces the indications for surgery. Although we assessed patients with negative magnetic resonance (MR) images, several prior investigations have explored this issue as part of their presurgical evaluations of positive, negative, or equivocal MR images [18-23]. It has been noted that in the case of congruent results of FDG-PET hypometabolism in patients with negative MRI findings and temporal lobe epilepsy with the electroclinical seizure onset zone, their seizure outcomes are similar to those with a positive MRI showing a lesion [18, 19].

As we noted, in the current study on patients with normal MRI results, 65.60% of patients exhibited seizure foci in temporal lobe, with 67.96% showing congruent PET results. Conversely, 25.4% had foci in frontal lobe, yet only 12.5% displayed congruent PET results. In line with our current findings, a prior study utilized FDG-PET of the brain to localize the epileptogenic focus in patients with negative MRI findings. They discovered that 62.5% of patients with a temporal lobe epileptogenic focus exhibited exact congruency with PET results, while only 29.7% displayed incongruence. However, individuals with a frontal lobe epileptogenic focus demonstrated only 6.6% exact congruency and 13.3% partial congruency. Among patients with a partially localized seizure focus, only 6.6% exact congruency and 53.3% incongruency were noted. The study highlighted that while PET results were not promising for frontal lobe or partially localized seizures, a majority of temporal lobe seizure patients showed exact congruency with PET results [12].

As indicated earlier, the sensitivity of PET for visual assessment to distinguish the epileptogenic zone is moderate, at approximately 80% in temporal lobe epilepsy and 60–70% in extratemporal lobe epilepsy [23, 24]. Recent advances also seem to have significantly increased the sensitivity of this tool in localizing seizures. As shown by Steinbrenner et al., in 2022, FDG-PET showed distinct hypometabolism in 74% and 56% of patients with temporal lobe epilepsy and extratemporal epilepsy, respectively [25]. FDG-PET was also shown to be useful in presurgical decision-making in half of the patients and more beneficial in temporal versus extratemporal epilepsy groups. Thus, FDG PET/CT seems to be more efficient in localizing epilepsy zones in temporal lobe than in extratemporal lobe. Furthermore, we found a substantial interrater agreement for localizing seizure foci in temporal lobe. Consistent with our findings, in a meta-analysis including DRE patients who underwent FDG-PET and MRI, the pooled concordance rate for temporal lobe was 0.79 (95% CI: 0.63–0.92) [26]. Therefore, both the current study and the meta-analysis provided evidence supporting the substantial agreement in localizing seizure foci within temporal lobe, enhancing the reliability of this method in patients with DRE.

4.1. Limitations and Strengths

This study successfully used a multimodal approach involving clinical evaluations, VEM data, and FDG-PET results for a comprehensive assessment of seizure localization, augmenting the validity of the study. However, several limitations should be noted. First, the single-center design of the study may restrict the generalizability of the findings to broader populations or different healthcare settings. Second, the inherent subjectivity in interpreting imaging results by human raters introduces the potential for bias, which could impact the reliability of conclusions. In addition, we did not assess surgical outcomes. Therefore, further multicenter studies considering concise follow-ups for monitoring outcomes are recommended.

5. Conclusion

In this study, the majority of patients exhibited a seizure focus localized in temporal lobe, which was supported by congruent PET results. However, a notable proportion also showed frontal lobe involvement, with lower congruency rates. FDG PET/CT highlighted significant partial congruency and incongruency, complicating accurate localization. It has been noted that clinical and EEG evaluations complemented PET findings, particularly in cases where PET scans yielded negative results or partial localization, underscoring the importance of comprehensive assessment strategies in managing patients with epilepsy.

Declarations

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