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Original Investigation

Contribution of FDG-PET in Epilepsy Surgery: Consistency and Postoperative Results Compared with Magnetic Resonance Imaging and Electroencephalography

Epilepsi Cerrahisinde FDG-PET'in Katkısı: Manyetik Rezonans Görüntüleme, Elektroensefalorafi ve Cerrahi Sonrası Uyumluluk

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ABSTRACT

AIM: Surgery is a treatment option for medically intractable epilepsy patients. Abnormalities in regional cerebral glucose metabolism, as identified by 18-fluorodeoxyglucose positron emission tomography (FDG-PET) have predictive prognostic value in evaluating the outcome of epilepsy surgery. This study investigated the efficacy of FDG-PET for delineation of the epileptogenic zone (EZ) by comparing its consistency with other diagnostic tools and surgical outcome.

MATERIAL and METHODS: We analyzed the results of 121 consecutive patients evaluated for epilepsy surgery. FDG-PET results were crosschecked with magnetic resonance imaging (MRI) and electroencephalography (EEG) results, as well as postoperative outcome and pathology.

RESULTS: FDG-PET findings of 75 patients (62 %) were concordant with MRI (Mc-Nemar-$\chi2$ test p=0.024, Kappa=0.22). Further, the PET findings were consistent with EEG, and was statistically significant, according to Post-hoc test, in temporal epilepsy (TLE) group ($\chi2$=8.21 P=0.04). Both investigations revealed localizing information in 56 (46.2%) patients. Twenty-six (72.2%) MRI-negative patients had hypometabolism on PET. The pathology of the 10 PET-negative patients was 5 cases of mesial temporal sclerosis, 2 cortical dysplasia, 2 gliosis and one tumor. Seven (70%) of these patients' lesions originated from the temporal lobe. FDG-PET had correctly predicted the EZ in 37 (86%) of 43 patients who underwent surgery.

CONCLUSION: FDG-PET results may not be strongly associated with EZ but represent an additional tool in delineation of EZ during the noninvasive phase of presurgical evaluation.

KEYWORDS: Intractable epilepsy, Positron emission tomography, Surgery, Prognosis

ÖZ

AMAÇ: Epilepsi cerrahisi, medikal tedaviye dirençli epilepsi hastalarında bir tedavi seçeneğidir. Dirençli epilepside 18-floro-deoksiglukoz pozitron emisyon tomografisiyle (FDG-PET) serebral glukoz metabolizma anomalilerinin, cerrahi prognozun öngörülmesinde belirleyici değeri mevcuttur. Çalışmada, FDG-PET sonuçlarının diğer tanısal araçlar ve cerrahi sonuçlarının karşılaştırılmasıyla epileptojenik alan (EA)'ın sınırlarının belirlenmesindeki etkinliğini araştırılmıştır.

YÖNTEM ve GEREÇLER: Çalışmada, epilepsi cerrahisi amaçlı incelenen 121 hastanın FDG-PET, manyetik rezonans görüntüleme (MRI) ve elektroensefalografi (EEG) sonuçları değerlendirilmiştir. FDG-PET sonuçları MRI ve EEG sonuçlarıyla uyumluluğuna bakılmış, postoperatif cerrahi sonuçları ve patolojiyle karşılaştırılmıştır. FDG-PET görüntüleri, bölgesel hipometabolik alanlar değerlendirilerek, genişliğe bakılmadan incelenmiştir.

BULGULAR: 75 hastanın (%62) FDG-PET sonuçları MRI sonuçlarıyla uyumlu olarak tespit edildi. (Mc-Nemar-$\chi2$ test p=0,024; Kappa=0,22) Özellikle temporal lob epilepsi (TLE) grubunda PET, EEG post-hoc test sonuçlarına göre ($\chi2$=8,21 P=0,04) istatistiksel anlamlı düzeyde uyumluydu. 56 hastada (%46,2) her iki tetkik epileptojenik alanı lokalize edebildi. 26 MRI-negatif hastanın (%72,2) PET görüntülemelerinde hipometabolizma mevcuttu. PET-negatif 10 hastanın patoloji sonuçları; 5 hipokampal skleroz, 2 kortikal displazi, 2 gliozis ve 1 tümör olarak kaydedildi. Bu hastaların 7'sinde lezyon (%70) temporal bölgeden kaynaklanmaktaydı. Epilepsi cerrahisi uygulanan 43 hastanın 37'sinde (%86) FDG-PET, EA'yı doğru olarak gösterdi.

SONUÇ: FDG-PET, değerlendirilen tüm hastalarda EA'yı göstermede güçlü bir yöntem olmamakla birlikte, cerrahi sınırları belirlemeden çok cerrahi öncesi non-invaziv EA'nın değerlendirmesinde yardımcı olarak kullanılabilecek faydalı bir tetkiktir.

ANAHTAR SÖZCÜKLER: Dirençli epilepsi, Pozitron emisyon tomografisi, Cerrahi, Prognoz

INTRODUCTION

Epilepsy is a heterogeneous group of disorders, with variations in seizure types, age of onset, and underlying pathology. Functional and structural imaging techniques are crucial in the evaluation of patients with epilepsy, especially those who are candidates for surgery. In patients with medically intractable focal epilepsy assessed for surgery, single-photon emission computed tomography (SPECT) (11) and positron emission tomography (PET) (12) can assist in the localization of the epileptogenic zone (EZ). The most commonly used radioactive ligand in PET studies is 2-[18F] Fluoro-2-deoxy-D-glucose (FDG) (16). Because of the short half-life and the relatively long uptake time of FDG, FDGPET studies are performed during the interictal period. Interictal FDG-PET scans demonstrate the decrease in glucose uptake, a seminal observation regarding FDG-PET and focal epilepsy made in 1980 by Kuhl, Engel and their colleagues (12). In the interictal state, there is a reduction in the local cerebral metabolic rate for glucose utilization (CMRGlu) in the epileptogenic zone (EZ) (8). While focal seizures cause a local increase, generalized absence seizures lead to a global increase in glucose metabolism (8). A recent study has shown that temporal glucose hypometabolism increases with the duration of epilepsy (20). Lee et al. investigated 33 patients with cryptogenic neocortical epilepsy, and found that FDGPET provided accurate localization of the ictal onset zone, as assessed by intra-cranial EEG recordings, in only 55% of cases (13). On the other hand, most of the falsely localized metabolic abnormalities were encountered in patients with extra-temporal seizures. Accordingly, in another study of 41 patients with cryptogenic neocortical epilepsy, FDG-PET correctly localized the abnormalities in only 43% of cases (10).

The cornerstone of successful surgery for epilepsy is the careful and precise identification of the operationally defined EZ (7), the removal of which is expected to lead to freedom from seizures in the majority of patients (15). The decision algorithm for epilepsy surgery, however, is generally based on empirical and center-specific logistics. Today, most cases can be diagnosed non-invasively, especially when concordant EEG and MRI findings reveal a focus. Nevertheless, if non-invasive investigations reveal contradictory results, there may be a need for invasive intracranial EEG recordings with associated increased costs and complications. Thus, the search for noninvasive and cost-effective means of seizure localization has been an important field of research.

In this study, we aimed to identify the additional value of pre-surgical application of interictal FDG-PET for decisionmaking regarding the selection of candidates for epilepsy surgery.

MATERIAL and METHODS

Patients

A total of 121 consecutive patients (45 men, 76 women) with medically intractable epilepsy who were being evaluated for epilepsy surgery were included in the study. The mean age of the patients was 28.98 ± 11.53 years (range, 2-59 years). A standard presurgical evaluation protocol, including video electroencephalography (EEG), magnetic resonance imaging (MRI), PET, and neuropsychological and psychiatric investigations, was applied to all patients, and the results were discussed with neurology, neurosurgery, neuroradiology, and nuclear medicine specialists in a meeting held before surgery. Forty-three patients who were considered eligible for surgery were operated on at the time of the study. MRI, EEG, and PET findings of all patients were analyzed. Findings from the different methods were both compared with each other to evaluate consistency and with respect to outcome in patients who underwent surgery.

EEG

All candidates were admitted to the video-EEG monitoring unit (EMU) to record ictal and interictal activities to delineate the EZ. The international 10–20 system was used for tracing, with additional sphenoidal electrodes when necessary. Fifteen patients in whom the EZ could not be evaluated by noninvasive methods underwent subsequent evaluations using surgically placed intracranial electrodes. Localization of the EZ was primarily performed through video EEG interpretation, with other imaging modalities used to increase the accuracy of by labeling the results as either concordant or discordant. In case of conflicting results between evaluation modalities, results of extracranial EEG monitoring were primarily used for determining the placement of intracranial electrodes, which were used for further delineation of surgical resection margins with anatomo-electro-clinical correlation.

MRI

Standard MRI (1.5T) was performed with conventional spin–echo T1-weighted sagittal, T2-weighted axial, flair axial, oblique coronal, and flair oblique coronal sequences. Sections of 3-mm thickness were obtained from the oblique coronal plane of the temporal lobes perpendicular to the long axis of the hippocampus. All images were evaluated visually by an experienced neuroradiologist.

FDG-PET

FDG-PET studies were performed with a high-resolution PET/CT scanner (LSO HI-REZ Siemens). After 6 h of fasting, 5 mCi of 18F-FDG was injected intravenously, and patients were asked to lie still with their eyes closed in a quiet, dimly lit room during injection and for the following 40 minutes. The emission scan started at 40 min after injection and lasted for 15 min, and an 8 min transmission scan was subsequently acquired for the purpose of attenuation correction. All images were evaluated visually by experienced nuclear medicine specialists. The images were evaluated according to the localization and presence of hypometabolism more than 10%, compared to the other side.

Statistics

Sensitivity, specificity, positive and negative predictive values, and rates of false positive and false negative results for FDG-PET, were calculated with respect to MRI, EEG, and

Table I: Etiological Distribution of the Patients According to Location

	Temporal	Frontal	Parietal	Occipital	Diffuse	None	Total
HS	50	-	-	-	-	-	50
Gliosis	3	-			2	-	6
Double Pathology	-	-	-	-	2	-	2
Tumor	1	-	-	-	-	-	1
MCD	9	9	6	1	4	-	29
No Lesion	-	-	-	-	-	33	33
Total	63	9	6	2	8	33	121

***HS**, hippocampal sclerosis; **MCD,** malformation of cortical development.*

postoperative EZ results depending on successful outcome at least in 1 year follow up. In addition, McNemar chi-square and Kappa consistency tests were applied to reveal the differences and consistencies between PET and the other tests. The Pearson chi-square test was applied to compare consistencies between different areas. When more than two groups were compared, post-hoc test was applied. P values of <0.05 were considered statistically significant for all tests.

This study was approved by ethical committee of Cerrahpasa Medical Faculty in year 2008.

RESULTS

One hundred and twenty-one patients (45 men, 76 woman) with a mean age of 28.9±11.5 years were studied. Sixteen of the patients were under 16 years of age. The mean age at seizure onset was 10.5 ± 10 years.

Patients were classified in four groups according to the localization of the lesion on MRI, as follows, temporal, extratemporal (frontal, parietal, occipital), diffuse, and none (MRI-negative). There were 63 patients in the temporal, 17 patients in the extratemporal, 8 patients in the diffuse, and 33 patients in none group. According to the etiologies of the lesions, there were two patients with double pathologies: cortical dysplasia with periventricular heterotopia and mesial temporal sclerosis with encephalomalacia (Table I).

The Consistency of PET with EEG Results

PET findings of 56 (46.2%) patients showed consistency with EEG results where EEG localization is taken as EZ. Both EEG recordings and PET scans revealed localization information in 53 patients, whereas localization and lateralization was not detected in both investigations of the other three patients (Table II).

Table II: EEG and PET Results According to EEG Localization

	EEG Localizing	EEG non-localizing, non-lateralizing
PET Localizing	53	-
PET Normal	-	3

When EEG and PET results were analyzed with respect to lateralization, 90 (74.3%) patients showed consistent findings. The consistency of PET and EEG findings according to brain lobes with respect to lateralization were as follows, 80.3% consistent in the temporal lobes, 60% consistent in the frontal lobes, 66.6% consistent in the parietal lobes, and 58% consistent in the unidentifed group (Table III). We made a further analysis, regarding the lesions in the frontal, parietal and frontal lobes in the same group as extratemporal lesions, and categorized the data in three groups: temporal, extratemporal, and unidentified, the chi-square test results of this analysis was $\chi^2=8.21$; p=0.04, which was a statistically significant value. Additional analysis using the Post-hoc test revealed that this significance stemmed from the temporal group.

The Consistency of PET with MRI Findings

PET findings of 75 (62%) patients were consistent with MRI results. Normal PET and MRI results were obtained from 10 of these 74 patients (Table IV). Consistency was evaluated on the basis of localization and lateralization. The results, with data representing number of individual patients, are listed in Table II.

From these data, the following parameters were calculated: sensitivity: 0.85, specificity: 0.35, accuracy: 0.67, positive predictive value: 0.70, negative predictive value: 0.57, false negative rate: 15%, false positive rate: 65%. McNemar χ^2 test: p=0.024, Kappa=0.22.

According to the statistical analysis, the Kappa factor was found to be 0.22, and this indicated that the consistency between PET and MRI results was low. On the other hand, from the clinical point of view, the use of MRI results as a reference for PET results yield a significantly high sensitivity but a significantly low specificity. This same pattern was also evident in the false negative and false positive rates.

The consistency of the PET and MRI results according to brain lobes were as follows, 78.9% consistent in the temporal lobes, 50% in the frontal lobes, 50% in the parietal lobes and 32% in the unidentified (negative PET and MRI) group.

Table III: EEG and PET Results According to EEG Lateralization

PET	Temporal	Frontal	Parietal	None	Total
EEG					
EEG Lateralizing	80.3%	60%	66.6%	58%	90(74.3%)

Table IV: The Consistency of PET with MRI

	MRI (+)	MRI (-)	Total
PET (+)	75	26	101
PET (-)	10	10	20
Total	85	36	121

PET in MRI-Negative Patients

No abnormalities were detected on the MRI scans of 36 patients. Of these, 26 (72.2%) showed hypometabolism on their PET images. Hypometabolism was seen in the temporal lobe in 18 patients, the frontal lobe in one patient, the parietal lobe in one patient, and 6 patients had multilobar hypometabolism. Five patients underwent surgery. Of these, 4 had cortical dysplasia and 1 had hippocampal sclerosis. Three of the cortical dysplasias were located in the temporal lobe and 1 was located in the parietal lobe. We have noted that FDG-PET had localized each patient's EZ correctly.

PET-Negative Patients

The pathology in the 10 PET-negative patients was as follows: hippocampal sclerosis in 5, cortical dysplasia in 2, gliosis in 2 and tumor in 1.

The Consistency of PET with Surgery Results

Forty-three of the study patients underwent surgery, and PET correctly localized the EZ in 37 (86%) of these patients. Further, this localization was confirmed by histopathology and surgical outcome. There were 18 hippocampal sclerosis, 17 focal cortical dysplasias, 3 gliosis, 2 focal cortical dysplasias with hippocampal sclerosis and one from each of hypothalamic hamartoma, neurofibromatosis and tuberosclerosis. According to the Engel's classification of postoperative outcome (6), 32 patients were class 1, 5 patients were class 2, 3 patients were class 3, and 3 patients were class 4.

Examination of the consistency of the PET and EZ results according to brain lobes revealed a consistency of 81.1% in the temporal lobes, 50.0% in the frontal lobes, 50.0% in the parietal lobes, and 66.6% in multilobar group.

DISCUSSION

FDG-PET has long been used for presurgical evaluation. It reflects the functional deficit zone, which may be more diffuse than the EZ. Nevertheless, as a non-invasive method, it can be a valuable supplement to other tools such as video electroencephalography (VEEG) and MRI. Although a powerful technique, MRI is far from perfect as a diagnostic tool as 20-30% of potential surgical candidates with focal epilepsy have normal MRI (4). Variable results have been reported regarding the consistency between FDG PET and other diagnostic techniques. Won et al (22) evaluated the concordance rate between MRI and FDG PET in 118 patients (mainly adults) and found it to be 68%. In our study, we found the concordance rate to be 61.1%; slightly lower than but consistent with that found by Won et al. It has been reported that ipsilateral temporal hypometabolism is associated with good surgical outcome in patients with mesial temporal lobe epilepsy (5,14,17,21) This is in agreement with our findings, in that 81.1% of our patients who had ipsilateral temporal hypometabolism achieved good postoperative seizure outcome. In addition, the consistency of our PET results with MRI was 78.9% in the group overall. Several studies have reported that extratemporal cortical hypometabolism is associated with poor postoperative outcome (1,2,14,19). Our results are also in agreement with those of previous studies, with 50% consistency rates in the frontal and parietal lobes.

MRI has become indispensable for presurgical evaluation of patients with intractable epilepsy. Previous studies demonstrated a worse postoperative seizure outcome when no lesion was detected on MRI (9,18). Of potential surgical candidates with focal epilepsy, 20-30% have normal MRI (4). The clinical features and EEG findings of many patients with MRI-negative intractable epilepsy are insufficient for classifying the epilepsy as either temporal or extratemporal with confidence, or for lateralizing the seizure onset to one hemisphere with certainty. In those situations, the use of functional imaging tests such as PET should be considered as a means of obtaining additional evidence for distinguishing the subtypes of epilepsy or for lateralizing seizure onset to one hemisphere (3) In our study, 36 patients were MRI-negative and, hypometabolism was evident on PET images of 26 (72.2%) of these patients. In these patients, PET abnormality may be used to delineate the hypothetical EZ to guide the localization of intracranial electrode implantation.

We consider FDG PET scan results to be of potential use for increasing the confidence of the clinician regarding the decision of whether or not to recommend epilepsy surgery. We found that FDG PET provided additional information describing the EZ, which could be used to supplement the other diagnostic methods, in 77% of patients. It is clear that concordant data is vital for assessing the potential for a positive outcome from epilepsy surgery.

This study was a retrospective study and had certain limitations. Although the number of patients who underwent FDG-PET was satisfactory, the number who then underwent surgery was lower than expected; therefore, in order to achieve more solid implications, comparisons for consistency were mostly performed in all patients, including pending patients. When the number of surgical patients increases, the results will be better confirmed, on the basis of outcome and histopathology.

CONCLUSION

In conclusion, the FDG PET scan, a noninvasive method, is a useful tool for the delineation of the EZ for presurgical evaluation. It may be especially useful in MRI-negative patients for decisions regarding electrode placement other than delineation of surgical EZ, because with its 65% false positive rate, the decision of surgical EZ may be misled.

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