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Surgical outcome in patients with MRI-negative, PET-positive temporal lobe epilepsy

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ABSTRACT

Purpose: The purpose of this study was to determine the long-term surgical outcomes of magnetic resonance imaging (MRI)-negative, fluorodeoxyglucose positron emission tomography (FDG-PET)-positive patients with temporal lobe epilepsy (TLE) and compare them with those of patients with mesial temporal sclerosis (MTS).

Methods: One hundred forty-one patients with TLE who underwent anterior temporal lobectomy were included in the study. The surgical outcomes of 24 patients with unilateral temporal hypometabolism on FDG-PET without an epileptogenic lesion on MRI were compared with that of patients with unilateral temporal hypometabolism on FDG-PET with MTS on MRI (n = 117). The outcomes were compared using Engel's classification at 2 years after surgery. Clinical characteristics, unilateral interictal epileptiform discharges (IEDs), histopathological data and operation side were considered as probable prognostic factors.

Results: Class I surgical outcomes were similar in MRI-negative patients and the patients with MTS on MRI (seizure-free rate at postoperative 2 years was 79.2% and 82% in the MRI-negative and MTS groups, respectively). In univariate analysis, history of febrile convulsions, presence of unilateral IEDs and left temporal localization were found to be significantly associated with seizure free outcome. Multivariate analysis revealed that independent predictors of a good outcome were history of febrile convulsions and presence of unilateral IEDs.

Conclusion: Our results suggest that epilepsy surgery outcomes of MRI-negative, PET positive patients are similar to those of patients with MTS. This finding may aid in the selection of best candidates for epilepsy surgery.

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1. Introduction

Temporal lobe epilepsy (TLE) is one of the most medical treatment-resistant type of focal epilepsy in adults and surgical treatment may help approximately 70% of the patients become seizure free [1–3]. In the preoperative assessment of TLE cases, it is important that neuroradiological findings support the clinical and electrophysiological studies in identifying the epileptic focus.

The most frequent histopathological finding in TLE patients is mesial temporal sclerosis (MTS). The sensitivity and specificity of cranial magnetic resonance imaging (MRI) is quite high, about 80–97% [4,5]. Hippocampal sclerosis (HS) detected by MRI is among

Abbreviations: AED, antiepileptic drugs; ATL, anterior temporal lobectomy; AVM, arteriovenous malformation; CD, cortical dysplasia; CI, confidence interval; EEG, electroencephalography; FC, febrile convulsion; FDG-PET, fluorodeoxyglucose positron emission tomography; HM, hypometabolism; HS, hippocampal sclerosis; IED, interictal epileptiform discharge; MRI, magnetic resonance imaging; MTS, mesial temporal sclerosis; SGTCS, secondary generalized tonic-clonic seizures; TLE, temporal lobe epilepsy.

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the most important positive predictive factors known to affect postoperative outcome [6–8]. While MTS is seen in 58–72% of TLE cases, it has been determined that MRI is normal in approximately 16% of the cases [5,9,10].

Although it has been reported in recent years that 3 T MRI provides 20–48% increase in providing new or additional information in comparison to 1–1.5 T MRI, other neuroimaging methods are required in the preoperative assessment of MRI-normal cases [11,12]. Therefore, fluorodeoxyglucose (FDG)-positron emission tomography (PET) is routinely used in many epilepsy centers for preoperative assessment to identify the epileptic focus. PET is a type of nuclear medicine imaging with multiple purposes, and gives information both on local and general brain metabolism. Glucose metabolism is the most frequently measured parameter and 18 F-FDG is the most commonly used molecule for this purpose. As a characteristic finding of epilepsy, there is a regional decrease in glucose uptake (hypometabolism) during interictal period. The definitive cause of hypometabolism is not known. The general opinion is that cerebral hypometabolism reflects neuronal cell loss; however, in fact, rather than the real structural area, cerebral dysfunction is caused by decreased synaptic input and electrical activity arising from the dysfunctional cortex. Therefore, hypometabolism extends far beyond the margins of the epileptic focus in the temporal lobe. In the light of this information, it can be concluded that hypometabolism on PET scan shows dysfunctional neural network [13].

FDG-PET scans localize the seizure focus correctly in 85–90% of TLE patients. Regional hypometabolism is also identified in FDG-PET scans of 60–82% of MRI-negative patients [14–16]. At the same time, FDG-PET is useful in predicting surgical outcome. In a large meta-analysis, it was found that while ipsilateral hypometabolism showed a predictive value of 86% for good surgical outcome, the corresponding value was between 71% and 80% in patients with normal MRI findings [13]. Although the underlying physiopathology in these cases is not completely enlightened, it has been put forward that it is a different syndrome from MTS that can be surgically treated [5,17].

Although it is considered that the surgical outcomes of MRI-normal cases are worse than that of patients with MTS, the studies performed in recent years support the fact that if PET, electroencephalography (EEG) and the results of other preoperative assessments are consistent and identify a single focus, this group has similar results to MTS group. It has also been reported in many series that MRI-normal cases have better surgical outcomes in comparison to patients with MTS [13–18].

The purpose of this study was to determine the long-term surgical outcomes of MRI-negative, FDG-PET-positive TLE patients and compare them with those of patients with MTS.

2. Material and methods

Patients who were diagnosed with medically refractory TLE and underwent standard anterior temporal lobectomy (ATL) between 2006 and 2013 at Gazi University Medical Faculty Epilepsy Center were retrospectively evaluated. Among 167 patients aged more than 17 years, 141 cases with a postoperative follow-up period of at least 2 years and unilateral temporal hypometabolism on FDG-PET scan were included in the study. The same preoperative assessment protocol was used in all patients. The present study was approved by the Institutional Ethical Board of Gazi University Faculty of Medicine and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

As the first step of preoperative assessment, a detailed clinical and medical history of the patients was obtained, and all the patients underwent physical and neurological examination. Afterwards, all cases were monitored with scalp electrodes and additional anterior temporal electrodes using international 10–20 electrode system on 32-channel EEG until a sufficient number of typical seizures were recorded. If the rate of interictal epileptiform discharges (IEDs) were $\geq$80% in EEG recordings in one temporal lobe, the IEDs were considered unilateral. Temporal lobe localization and right/left lateralization of the patients were determined by correlating with ictal clinical signs and ictal and interictal EEG.

In all cases, cranial MRI was performed with temporal lobe epilepsy protocol using superconducting magnets with multichannel head coils in the supine position. While 1.5 T MRI (GE SIGNA EXCITE, Milwaukee, USA) was used in imaging in the first years of the study, assessments were performed by 3 T MRI (Siemens MagnetomVerio, Erlangen, Germany) in the last 4 years. Temporal lobe epilepsy protocol included axial and sagittal T1 weighted, axial T2 weighted, oblique coronal FLAIR perpendicular to the long axis of both hippocampi, and 3D inversion recovery (IR). The whole brain volumetric series were acquired using a 3D IR technique with a slice of 1 mm thickness, zero interslicegap, 256 $\times$ 222 matrix size, and a single signal average. T2 weighted oblique axial images through the long axis of both hippocampi consisting of 20 slices werealso obtained with 3 mm slice thickness and 0.75 mm interslice gap. All images were evaluated by experienced neuroradiologists.

Standard brain FDG-PET imaging protocol was used in all cases. The reconstruction of PET images was performed using FORE-OSEM iterative reconstruction method. Imaging was performed using Discovery ST (GE Medical Systems, Milwaukee, WI, USA) PET/CT camera system. Trans-axial and coronal PET images were prepared considering the AC/PC (anterior commissure/posterior commissure) line, and additional transverse sections were obtained according to temporal lobe plane. PET images were evaluated visually by 2 experienced nuclear medicine specialists independently without any knowledge on patients, surgery and follow-up results. Statistical parametric mapping (SPM) analysis was performed, if necessary. Consequently, FDG-PET images were classified into groups having right or left temporal hypometabolism. Cases with normal, bilateral or extratemporal PET findings were excluded. Patients with discordance regarding hypometabolism between ictal EEG and PET were also excluded.

All cases underwent psychiatric and neuropsychological assessment before surgery. None of the patients had a psychiatric disorder that was a definite contraindication for surgery, such as acute psychosis. Patients who were diagnosed with depression and anxiety disorder were followed-up with antidepressant therapy. All patients were administered a battery of neuropsychological tests by a neuropsychologist. Patients who were scheduled for surgery underwent WADA test or fMRI. Recently, fMRI rather than WADA was used reliably in most of the patients in our routine clinical practice, as is used in many epilepsy centers.

The results of preoperative assessment protocols were discussed in a multidisciplinary council, and if clinical and semiological findings, interictal and ictal EEG activities, and neuroimaging and neuropsychological assessments were consistent with each other and localize a single focus, surgery decision was made and the surgical technique was determined. ATL was performed for all patients by the same surgeon at the Department of Neurosurgery in our hospital. Standard anterior temporal resection was performed in all patients.

In the postoperative period, the patients were evaluated in terms of seizure state and antiepileptic drug (AED) use at 2 and 6 months, and thereafter once a year by the same epileptologist. In accordance with the AED withdrawal protocol of our clinic, the same drug treatment was continued for 6 months postoperatively in all patients. One of the AEDs was discontinued in patients who were seizure-free at the end of 6 months, by gradually decreasing the dose of the drug. Thereafter, the dose of the second drug was

also decreased, and all medications were stopped at the end of the 2nd year.

Engel seizure classification was used in the evaluation of postoperative outcomes [19] (Class I: free of disabling seizures, Class II: rare disabling seizures, Class III: worthwhile improvement, Class IV: no worthwhile improvement). For the analysis, the seizure-free group (Engel I) was compared with the group having seizures (Engel II, III, IV). The seizure state of the cases was followed up at 6 months, 1 and 2 years, and once a year after that.

2.1. Data collection

Various preoperative prognostic variables that may have an effect on predicting postoperative success were identified. These were age, gender, preoperative epilepsy duration, seizure type (the presence of secondary generalized tonic clonic seizures), temporal lobe lateralization, the presence of complicated febrile convulsions (FC), ipsilateral temporal IEDs, and the presence of unilateral HS on cranial MRI. Postoperative AED use and histopathological data were also recorded.

2.2. Statistical analysis

Data analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 16.0 for Windows. Data were expressed as mean ± standard deviation for continuous variables and as number and percentages for categorical variables. The mean differences between the groups were analyzed by Student's *t*-test. Categorical data were evaluated by Pearson's chi-square or Fisher's exact test, where applicable. A univariate logistic regression analysis was used to evaluate the potential prognostic factors having significant effects on surgical outcome. Any variable with a p value of <0.25 was accepted as a candidate for the multivariable model along with all variables of known prognostic clinical importance. In order to identify the best predictive factors, the factors that were found to be significant were included in a multivariate logistic regression model. Odds ratios, 95% confidence interval (CI) and the Wald statistics for each independent variable were also calculated for a seizure-free outcome at 2 years after the surgery and at the last follow-up. A p value of <0.05 was considered statistically significant.

3. Results

The demographic and clinical characteristics of 141 cases are presented in Table 1. The number of MRI-negative and MRI-positive cases was 24 (16.8%) and 117 (83%), respectively, and these cases were compared. While 1.5 T MRI was used for 45 cases, 3 T MRI was used for the remaining 96 cases. The number of MRI-negative cases was 9 (20%) by 1.5 T MRI and 15 (15.6%) by 3 T MRI; no significant difference was determined between the two groups ($p = 0.648$). Moreover, there was also no significant difference in terms of surgical results between the cases who underwent1.5 T MRI and 3 T MRI ($p = 0.145$).

FDG-PET images revealed that unilateral temporal hypometabolism was on the left in 79 (56%) cases, and on the right in 62 cases (44%).

While 127 (90.1%) of 141 cases were HS-positive, 14 (9.9%) of them were HS-negative. Pathological examination of MRI-negative patients revealed the following; 10 cases had HS (41.6%), 3 (12.5%) cases had cortical dysplasia (CD), 3 (12.5%) had tumors, 6 (25%) had gliosis and 2 (8.3%) cases had normal MRI findings.

While 79.2% of the patients were seizure-free in postoperative 2 years in the MRI-negative group, 82.2% of the patients were seizure-free in the MRI-positive group, and there was no statistically significant difference between the two groups ($p = 0.748$). In detail evaluation of the cases, 17 (70.8%) cases of the MRI-negative group and 86 (73.5%) cases of the MRI-positive group were seizure- and aura-free. Furthermore, mean age, gender distribution, seizure type, and seizure duration were similar in MRI-negative and positive groups at postoperative 2 years ($p > 0.05$). History of FC, unilateral IEDs, HS, and left temporal lobe localization were significantly frequent in the MRI-positive group when compared to the MRI-negative group ($p = 0.03$, $p = 0.045$, $p = 0.05$, and $p = 0.045$, respectively). Five cases were performed invasive monitoring with subdural strip and grids in the MRI-negative group. There was no statistically significant difference in terms of surgical outcomes between cases that underwent invasive EEG monitoring or not ($p = 0.192$).

Table 1
Demographic and baseline characteristics of the study patients.

	PET+/MRI− $n = 24$	MTS $n = 117$	p value
Age	29.2 ± 7.38	28.6 ± 8.85	0.452
Gender			0.415
Female	13 (54.2)	69 (59)	
Male	11 (45.8)	48 (41)	
Mean duration of epilepsy, years			0.218
<11	7 (29.2)	30 (25.6)	
11–20	8 (33.3)	60 (51.3)	
>20	9 (37.5)	27 (23.1)	
FC	9 (37.5)	72 (61.5)	**0.030**
Side of surgery			**0.045**
Left	7 (29.2)	72 (61.5)	
Right	17 (70.8)	45 (38.5)	
Seizure			0.308
CPS + SGTCS	21 (87.5)	94 (80.3)	
CPS	3 (12.5)	23 (19.7)	
EEG-IEDs			**0.045**
Bilateral	9 (37.5)	24 (17.0)	
Unilateral	15 (10.6)	93 (66)	
Pathological data			
HS (−)	5 (20.8)	9 (7.7)	**0.050**
HS (+)	19 (79.2)	108 (92.3)	

Bold characteristics are statistically significant values.

Univariate logistic regression analysis was used to evaluate whether potential factors had a statistically significant effect on postoperative outcome. This analysis was performed separately for the PET-positive/MRI-negative and MTS groups. The results of univariate logistic regression analysis of factors that may have an effect on seizure-freedom (Engel I) of cases that were followed-up for at least two years are presented in Table 2. The positive predictive factors of seizure freedom after surgery were history of FC, unilateral IEDs, and left temporal localization.

These variables having a prognostic effect according to single variable logistic regression analysis were entered into multivariate logistic regression model (Table 3). According to the results of final analysis, left temporal localization had no effect on seizure-freedom and only the presence of unilateral IEDs and history of complicated FC were found to be the independent prognostic factors predicting good surgical outcome

4. Discussion

In the present study, we reported the surgical outcomes of MRI-negative PET-positive cases. Our results suggest that MRI-negative, PET-positive cases also benefit from surgical treatment. At postoperative 2 years, 79.2% of the cases were Engel class I. When these results were compared with that of MTS group that is known to have good surgical outcome, again similar results were achieved. Our results support the other studies that reported quite high postoperative seizure-free rates in MRI-negative PET-positive

Table 2
Univariate analysis of variables at postoperative 2 years for seizure-free outcome.

	PET+/MRI−				MTS			
	SF ($n=19$)	NSF ($n=5$)	p value	OR (95% CI)	SF ($n=96$)	NSF ($n=21$)	p value	OR (95% CI)
Age, years	28.3 ± 4.35	27.4 ± 2.54	0.645	0.99 (0.95–1.03)	28.9 ± 3.37	27.0 ± 5.73	0.489	0.98 (0.93−1.03)
Gender			0.585	1.15 (0.55–2.42)			0.150	1.60 (0.64–2.81)
Female	10 (41.7)	3 (12.5)			54 (46.2)	15 (12.8)		
Male	9 (37.5)	2 (8.3)			42 (35.9)	6 (5.1)		
Side of operation			0.146	1.00 (0.90–1.09)			**0.044**	2.44 (1.02–5.10)
Left	7 (29.2)	–			54 (46.2)	18 (15.4)		
Right	12 (50)	5 (20.8)			42 (35.9)	3 (2.6)		
Seizure			0.479	1.05 (0.90–1.44)			0.366	1.67 (0.69–4.22)
CPS + SGTCS	16 (66.7)	5 (20.8)			76 (65)	18 (15.4)		
CPS	3 (12.5)	–			20 (17.1)	3 (2.6)		
EEG-IEDs			**0.047**	0.20 (0.08–0.96)			**<0.001**	3.27 (1.20–8.10)
Bilateral	5 (20.8)	4 (16.7)			10 (8.5)	12 (10.3)		
Unilateral	14 (58.3)	1 (4.2)			86 (73.5)	9 (7.7)		
Duration of epilepsy								
<11	5 (20.8)	2 (8.3)	0.201	1.05 (0.23–4.04)	25 (21.4)	5 (4.3)	0.978	1.50 (0.70–3.55)
11–20	8 (33.3)	–			49 (41.9)	11 (9.4)		
>20	6 (25)	3 (12.5)			22 (18.8)	5 (4.3)		
Pathological data			0.270	1.68 (0.60–3.55)			0.506	1.60 (0.50–4.92)
HS (−)	3 (12.5)	2 (8.3)			7 (6.0)	2 (1.7)		
HS (+)	16 (66.7)	3 (12.5)			89 (76.1)	19 (16.2)		
FC	10 (41.7)	–	**0.047**	1.56 (1.05–2.30)	67 (57.3)	5 (4.3)	**<0.001**	3.17 (1.20–7.82)

Bold characteristics are statistically significant values.
Data are presented as mean ± standard deviation or number (%), where appropriate.
OR: odds ratio, CI: confidence interval; SF: seizure-free; NSF: non seizure-free; CPS: complex partial seizure; SGTCS: secondarily generalized tonic-clonic seizure; EEG: electroencephalography; IEDs: interictal epileptiform discharges; MRI: magnetic resonance imaging; HS: hippocampal sclerosis; FC: febrile convulsion; FDG-PET: fluorodeoxyglucose-positron emission tomography.

cases [5,17,20]. In these studies, MRI-negative PET-positive cases were compared with MTS cases and were found to have similar seizure-free rates as was in our study. While MRI is the most important diagnostic factor in preoperative assessments of resistant TLE cases, it has been shown that only FDG-PET was successful in predicting surgical outcome [21].

There are also studies and meta-analysis reporting much worse surgical outcomes in non lesional TLE cases compared to MTS group in the literature [3,22]. It was reported in these studies that the best predictive factors were positive PET results and consistent EEG and PET results, however, as is in our study, MRI-negative PET positive sub-group was not compared with MTS group. Another meta-analysis stated that ipsilateral PET hypometabolism in preoperative assessments is a good indicator for surgical outcome and is more valuable if MRI is normal [13].

The preoperative approach in MRI-negative patients is another topic of discussion. These cases are recommended to undergo preoperative invasive EEG monitoring in many centers. However, in the recent years especially after the widespread clinical use of FDG-PET, this understanding is changing. It has been previously known that seizure onset on scalp and invasive EEG is correlated with unilateral hypometabolism on PET [23]. Among cases undergoing invasive EEG monitoring, surgical outcomes of PET-positive cases are better. Invasive EEG monitoring is gold standard when there are difficulties or conflicts in noninvasive assessments [24–27]. The demonstration that excellent surgical outcomes are achieved in TLE cases, if IED and ictal EEG findings on noninvasive EEG are consistent with PET findings has led to a new understanding [15,28,29]. In the light of this information, the need for invasive EEG during preoperative assessments is decreasing and thus high cost and complication risk is minimized. It was observed in our study that there was no difference in the surgical outcomes of patients who had undergone invasive EEG recording or not. Therefore, in our center, if clinical data, scalp ictal and interictal EEG and FDG-PET findings of resistant TLE cases were consistent with each other and localize a single focus, the patients were considered as surgical candidates without performing an invasive intervention.

The underlying physiopathology in MRI-negative, PET-positive TLE cases remain unclear. It has been previously reported that when FDG-PET findings and pathology results of MTS cases are evaluated together, hypometabolism is not correlated with the degree of hippocampal cell loss [30]. Similarly, HS and degree of temporal atrophy on MRI scans of MTS cases were not correlated with the topography of hypometabolism on FDG-PET [31]. The major importance of the degree of focal hypometabolism on FDG-PET is its role in predicting good surgical outcome [32]. Temporal hypometabolism is not associated with the degree of hippocampal damage measured by MRI or evaluated by histopathological examinations, because the degree of hypometabolism does not change in mild, moderate or severe damages. Therefore, even if MRI is normal or shows mild hippocampal abnormality, PET may

Table 3
Multivariate stepwise logistic regression analysis at 2 years after epilepsy surgery for seizure-free outcome.

	OR	95% CI		Wald	p
		Lower limit	Upper limit		
Unilateral IED	223.857	6.030	311.049	8.610	**0.003**
FC	33.098	3.526	310.720	9.380	**0.002**
Left temporal localization	1.422	0.189	10.716	0.117	0.733

Bold characteristics are statistically significant values.
OR: odds ratio, CI: confidence interval; IED: interictal epileptiform discharge; FC: febrile convulsion.

show significant hypometabolism. In conclusion, although FDG-PET is quite effective in localizing the epileptic region, it can be considered that it is not sensitive in reflecting HS severity [26].

Different theories are proposed on the underlying pathology. These cases are reported to be associated with small temporal pole encephaloceles or microscopic cortical dysplasia [33,34]. In another research, PET hypometabolism in MRI-negative cases was not associated with HS but with hippocampal structural abnormalities (gliosis, heterotopic neurons) [35]. Another researcher group claimed that the absence of hippocampal atrophy in MRI-negative patients was caused by the presence of neocortical abnormalities in the lateral temporal lobe rather than in the mesial region. Furthermore, they proposed that these cases represent a different entity than MTS showing good response to surgical treatment [17].

In many studies performed to date, the probability of seizure free outcome in cases after TLE surgery was based on histopathology and MRI findings. In a very recent large-scale study performed on medical treatment resistant TLE cases, a new pathological classification was recommended for HS. Different from the current classification, ''No-HS/gliosis only'' classification is recommended for cases without HS but with normal neurons and reactive gliosis [36]. Likewise, in our study, while the majority of the cases had HS, lower number of histopathologies like tumors, CD, arteriovenous malformations (AVM) and nonspecific gliosis were observed.

Our results demonstrated that history of FCs and IEDs were the most important clinical factors affecting postoperative seizure-free state. Likewise, some studies have previously demonstrated that FC has a positive predictive value on surgical outcome [37,38]. Observing good surgical outcomes in the presence of history of febrile seizures might be attributed to a relation with MTS. Although there is no precise evidence that prolonged FC is a risk factor for mesial temporal sclerosis, there is an unquestionable strong relationship between these two conditions. It has been hypothesized that FS also influences expression and/or function of other ion channels that are known to control hippocampal excitability. Pronounced changes have been already found in hippocampal excitatory and inhibitory ligand-gated ion channels. It has been suggested that seizure-induced changes in gamma-aminobutyric acid -A receptor (GABAAR)-mediated neurotransmission may compromise the gatekeeper function of the dentate gyrus and contribute to hippocampal hyperexcitability accompanying the process of epileptogenesis [39].

Although there was no difference in the frequency of IEDs between the 2 groups in our study, unilateral IEDs were found to be one of the most effective factors on outcome, and similar results were also found in the literature [40,41]. Similar to our study, independent of HS identified on MRI, electrophysiological studies were previously shown to affect prognosis [42]. On the contrary, some researchers determined that IEDs failed to predict long-term outcome [43,44]. If unilateral IEDs are localized to the temporal lobe operated and particularly if the localization degree is high, they predict postoperative good results. Contrarily, diffuse interictal discharges suggest diffuse irritative zone that shows bad prognosis. A prospective study showed the seizure rates increased by 80% in patients with $\geq$90% predominance on the operation side in postoperative long-term follow-up, but seizure-free rate was 54% if IEDs show lesser degrees of lateralization [45]. In case of detection a small interictal epileptogenic area particularly localized in the anterior temporal area and in case of a history of FC, despite quite successful surgical outcomes, long seizure duration and presence of etiological factors such as history of a head trauma or meningitis leading to diffuse lesions cause secondary epileptogenesis, which results in bilateral IEDs and poor prognosis [46,47]. Starting from this information, if MRI is normal and findings indicating a diffuse lesion are determined in EEG, invasive assessments are required.

Our study is limited due to its retrospective design; however, this is true for numerous other surgical outcome studies. Performing prospective studies on epilepsy surgery is difficult because of individual decisions substituting randomization. Although our series is quite large, the number of cases is limited as MRI-negative PET-positive cases are a highly selected group. Because, very strict rules were applied in terms of clinical, electrophysiological, and neuroimaging methods in the preoperative assessments, in the selection of this group of patients with quite complicated diagnosis, and cases not conforming to these rules were not considered as surgical candidates. Increase in the number of studies on this topic in the future, will result in changes in treatment strategies of MRI-negative patients and increase the number of surgical cases. In order to obtain definitive results, larger patient groups and a longer postoperative follow-up period is necessary.

5. Conclusions

Our results support surgical treatment in MRI-normal PET-positive TLE cases and approximately more than 2/3 of these cases are seizure-free. This information will help to abandon the presumption that surgery should not be performed in MRI-normal cases. A single test is not adequate for precise surgical localization in TLE patients, and the use of multiple tests together provides higher precision localization and the tests verify each other. Particularly, when EEG recordings, PET scan and neuropsychological tests localize a single focus, surgical results are similar to that of mesial TLE. Therefore, PET-positive MRI-negative cases are different from classic HS cases, but this can be considered a clinical syndrome having a similar good response to surgery. In this way, it is possible to be successful in seizure control of a carefully selected patient group.

Conflict of Interest

None.

Role of the funding source

None.

References

[1] Engel Jr J. Surgery for seizures. N Engl J Med 1996;334:647–52.
[2] McIntosh AM, Wilson SJ, Berkovic SF. Seizure outcome after temporal lobectomy: current research practice and findings. Epilepsia 2001;42:1288–307.
[3] Téllez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain 2005;128:1188–98.
[4] Kuzniecky RI, Bilir E, Gilliam F, Faught E, Palmer C, Morawetz R, et al. Multimodality MRI in mesial temporal sclerosis: relative sensitivity and specificity. Neurology 1997;49:774–8.
[5] LoPinto-Khoury C, Sperling MR, Skidmore C, Nei M, Evans J, Sharan A, et al. Surgical outcome in PET-positive, MRI-negative patients with temporal lobe epilepsy. Epilepsia 2012;53:342–8.
[6] McIntosh AM, Kalnins RM, Mitchell LA, Fabinyi GC, Briellmann RS, Berkovic SF. Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence. Brain 2004;127:2018–30.
[7] Spencer SS, Berg AT, Vickrey BG, Sperling MR, Bazil CW, Shinnar S, et al. Predicting long-term seizure outcome after resective epilepsy surgery: the multicenter study. Neurology 2005;65:912–8.
[8] Gilliam F, Bowling S, Bilir E, Thomas J, Faught E, Morawetz R, et al. Association of combined MRI, interictal EEG, and ictal EEG results with outcome and pathology after temporal lobectomy. Epilepsia 1997;38:1315–20.
[9] Wiebe S, Blume WT, Girvin JP, Eliasziw M, Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med 2001;345:311–8.

[10] Berkovic SF, McIntosh AM, Kalnins RM, Jackson GD, Fabinyi GC, Brazenor GA, et al. Preoperative MRI. predicts outcome of temporal lobectomy: an actuarial analysis. Neurology 1995;45:1358–63.
[11] Phal PM, Usmanov A, Nesbit GM, Anderson JC, Spencer D, Wang P, et al. Qualitative comparison of 3-T and 1.5-T MRI in the evaluation of epilepsy. AJR Am J Roentgenol 2008;191:890–5.
[12] Schmitz BL, Aschoff AJ, Hoffmann MH, Grön G. Advantages and pitfalls in 3T MR brain imaging: a pictorial review. AJNR Am J Neuroradiol 2005;26:2229–37.
[13] Willmann O, Wennberg R, May T, Woermann FG, Pohlmann-Eden B. The contribution of 18F-FDG PET in preoperative epilepsy surgery evaluation for patients with temporal lobe epilepsy: a meta-analysis. Seizure 2007;16:509–20.
[14] Casse R, Rowe CC, Newton M, Berlangieri SU, Scott AM. Positron emission tomography and epilepsy. Mol Imaging Biol 2002;4:338–51.
[15] Gok B, Jallo G, Hayeri R, Wahl R, Aygun N. The evaluation of FDG-PET imaging for epileptogenic focus localization in patients with MRI positive and MRI negative temporal lobe epilepsy. Neuroradiology 2013;55:541–50.
[16] Henry TR, Van Heertum RL. Positron emission tomography and single photon emission computed tomography in epilepsy care. Semin Nucl Med 2003;33: 88–104.
[17] Carne RP, O'Brien TJ, Kilpatrick CJ, MacGregor LR, Hicks RJ, Murphy MA, et al. MRI-negative PET-positive temporal lobe epilepsy: a distinct surgically remediable syndrome. Brain 2004;127:2276–85.
[18] Vinton AB, Carne R, Hicks RJ, Desmond PM, Kilpatrick C, Kaye AH, et al. The extent of resection of FDG-PET hypometabolism relates to outcome of temporal lobectomy. Brain 2007;130:548–60.
[19] Engel Jr J, Van Ness PC, Rasmussen T, Ojemann LM. Outcome with respect to epileptic seizures. In: Engel Jr J, editor. Surgical treatment of epilepsies. New York: Raven Press; 1993. p. 609–21.
[20] Alarcón G, Valentín A, Watt C, Selway RP, Lacruz ME, Elwes RD, et al. Is it worth pursuing surgery for epilepsy in patients with normal neuroimaging? J Neurol Neurosurg Psychiatry 2006;77:474–80.
[21] Struck AF, Hall LT, Floberg JM, Perlman SB, Dulli DA. Surgical decision making in temporal lobe epilepsy: a comparison of [(18)F]FDG-PET, MRI, and EEG. Epilepsy Behav 2011;22:293–7.
[22] Immonen A, Jutila L, Muraja-Murro A, Mervaala E, Äikiä M, Lamusuo S, et al. Long-term epilepsy surgery outcomes in patients with MRI-negative temporal lobe epilepsy. Epilepsia 2010;51:2260–9.
[23] Delbeke D, Lawrence SK, Abou-Khalil BW, Blumenkopf B, Kessler RM. Post-surgical outcome of patients with uncontrolled complex partial seizures and temporal lobe hypometabolism on 18FDG-positron emission tomography. Invest Radiol 1996;31:261–6.
[24] Valk PE, Laxer KD, Barbaro NM, Knezevic S, Dillon WP, Budinger TF. High-resolution (2.6-mm) PET in partial complex epilepsy associated with mesial temporal sclerosis. Radiology 1993;186:55–8.
[25] Salanova V, Markand O, Worth R, Smith R, Wellman H, Hutchins G, et al. FDG-PET and MRI in temporal lobe epilepsy: relationship to febrile seizures, hippocampal sclerosis and outcome. Acta Neurol Scand 1998;97:146–53.
[26] Lamusuo S, Jutila L, Ylinen A, Kälviäinen R, Mervaala E, Haaparanta M, et al. [18F]FDG-PET reveals temporal hypometabolism in patients with temporal lobe epilepsy even when quantitative MRI and histopathological analysis show only mild hippocampal damage. Arch Neurol 2001;58:933–9.
[27] Theodore WH, Carson RE, Andreasen P, Zametkin A, Blasberg R, Leiderman DB, et al. PET imaging of opiate receptor binding in human epilepsy using [18F]cyclofoxy. Epilepsy Res 1992;13:129–39.
[28] Salanova V, Markand O, Worth R. Focal functional deficits in temporal lobe epilepsy on PET scans and the intracarotid amobarbital procedure: comparison of patients with unitemporal epilepsy with those requiring intracranial recordings. Epilepsia 2001;42:198–203.
[29] Henry TR, Roman DD. Presurgical epilepsy localization with interictal cerebral dysfunction. Epilepsy Behav 2011;20:194–208.
[30] Foldvary N, Lee N, Hanson MW, Coleman RE, Hulette CM, Friedman AH, et al. Correlation of hippocampal neuronal density and FDG-PET in mesial temporal lobe epilepsy. Epilepsia 1999;40:26–9.
[31] Chassoux F, Semah F, Bouilleret V, Landre E, Devaux B, Turak B, et al. Metabolic changes and electro-clinical patterns in mesio-temporal lobe epilepsy: a correlative study. Brain 2004;127:164–74.
[32] Dupont S, Semah F, Clémenceau S, Adam C, Baulac M, Samson Y. Accurate prediction of postoperative outcome in mesial temporal lobe epilepsy: a study using positron emission tomography with 18fluorodeoxyglucose. Arch Neurol 2000;57:1331–6.
[33] Abou-Hamden A, Lau M, Fabinyi G, Berkovic SF, Jackson GD, Mitchell LA, et al. Small temporal pole encephaloceles: a treatable cause of "lesion negative" temporal lobe epilepsy. Epilepsia 2010;51:2199–202.
[34] Diehl B, LaPresto E, Najm I, Raja S, Rona S, Babb T, et al. Neocortical temporal FDG-PET hypometabolism correlates with temporal lobe atrophy in hippocampal sclerosis associated with microscopic cortical dysplasia. Epilepsia 2003;44:559–64.
[35] Bien CG, Szinay M, Wagner J, Clusmann H, Becker AJ, Urbach H. Characteristics and surgical outcomes of patients with refractory magnetic resonance imaging-negative epilepsies. Arch Neurol 2009;66:1491–9.
[36] Blümcke I, Thom M, Aronica E, Armstrong DD, Bartolomei F, Bernasconi A, et al. International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: a Task Force report from the ILAE Commission on Diagnostic Methods. Epilepsia 2013;54:1315–29.
[37] Hennessy MJ, Elwes RD, Rabe-Hesketh S, Binnie CD, Polkey CE. Prognostic factors in the surgical treatment of medically intractable epilepsy associated with mesial temporal sclerosis. Acta Neurol Scand 2001;103:344–50.
[38] Elsharkawy AE, Alabbasi AH, Pannek H, Oppel F, Schulz R, Hoppe M, et al. Long-term outcome after temporal lobe epilepsy surgery in 434 consecutive adult patients. J Neurosurg 2009;110:1135–46.
[39] Swijsen A, Avila A, Brône B, Janssen D, Hoogland G, Rigo JM. Experimental early-life febrile seizures induce changes in GABA(A) R-mediated neurotransmission in the dentate gyrus. Epilepsia 2012;53:1968–77.
[40] Salanova V, Andermann F, Rasmussen T, Olivier A, Quesney L. The running down phenomenon in temporal lobe epilepsy. Brain 1996;119:989–96.
[41] Chung MY, Walczak TS, Lewis DV, Dawson DV, Radtke R. Temporal lobectomy and independent bitemporal interictal activity: what degree of lateralization is sufficient? Epilepsia 1991;32:195–201.
[42] Radhakrishnan K, So EL, Silbert PL, Jack Jr CR, Cascino GD, Sharbrough FW, et al. Predictors of outcome of anterior temporal lobectomy for intractable epilepsy: a multivariate study. Neurology 1998;51:465–71.
[43] Aull-Watschinger S, Pataraia E, Czech T, Baumgartner C. Outcome predictors for surgical treatment of temporal lobe epilepsy with hippocampal sclerosis. Epilepsia 2008;49:1308–16.
[44] Jeong SW, Lee SK, Kim KK, Kim H, Kim JY, Chung CK. Prognostic factors in anterior temporal lobe resections for mesial temporal lobe epilepsy: multivariate analysis. Epilepsia 1999;40:1735–9.
[45] Paglioli E, Palmini A, Paglioli E, da Costa JC, Portuguez M, Martinez JV, et al. Survival analysis of the surgical outcome of temporal lobe epilepsy due to hippocampal sclerosis. Epilepsia 2004;45:1383–91.
[46] Tonini C, Beghi E, Berg AT, Bogliun G, Giordano L, Newton RW, et al. Predictors of epilepsy surgery outcome: a meta-analysis. Epilepsy Res 2004;62: 75–87.
[47] Holmes MD, Born DE, Kutsy RL, Wilensky AJ, Ojemann GA, Ojemann LM. Outcome after surgery in patients with refractory temporal lobe epilepsy and normal MRI. Seizure 2000;9:407–11.