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Intractable Temporal Lobe Epilepsy: Comparison of Positron Emission Tomography with Qualitative and Quantitative MR

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PURPOSE: To compare the ability of qualitative fludeoxyglucose F 18 positron emission tomography (QPET), qualitative MR imaging (QMR), and quantitative MR imaging with hippocampal formation volumetric assessment (HV MR) to lateralize the seizure focus in patients with temporal lobe epilepsy. **METHODS:** Sixteen consecutive patients undergoing presurgical examination for temporal lobe seizures had QPET, QMR, and HV MR. The presence of temporal lobe epilepsy was confirmed by Engel class I or II outcomes at 1-year postoperative follow-up examinations. A QPET, QMR, or HV MR study was considered to be lateralizing if it matched the side of the seizure focus, nonlateralizing if it did not lateralize the seizure focus to either temporal lobe, or incorrectly lateralizing if it lateralized the seizure focus to the incorrect side. **RESULTS:** Of 16 patients with proved temporal lobe seizures, QPET was correctly lateralizing in nine (56%), nonlateralizing in six (37.5%), and incorrectly lateralizing in one (6%). QMR was correctly lateralizing in six (37.5%), nonlateralizing in six (37.5%), and incorrectly lateralizing in four (25%). HV MR was correctly lateralizing in all 16 patients (100%). Age at onset, seizure duration, and total number of seizures did not correlate with QPET, QMR, and HV MR lateralization. **CONCLUSIONS:** Our results show that each imaging technique yields useful information for seizure lateralization in temporal lobe epilepsy and that HV MR yields considerably more information than QPET or QMR.

Index terms: Brain, magnetic resonance; Brain, measurements; Hippocampus; Positron emission tomography; Seizures

Patients with intractable complex partial seizures of temporal lobe origin account for a substantial percentage of all patients with refractory epilepsy who are referred for surgery (1). Lateralization and localization of the focus are essential to the success of seizure surgery (2).

Ictal electroencephalographic (EEG) data recorded from scalp/sphenoidal electrodes and, more recently, surgically implanted electrodes have been the standard method for clinical lateralization and localization of seizure foci (3, 4). Invasive EEG and electrocorticographic data have been found to correlate strongly with true seizure focus as determined by successful outcome of seizure surgery (5–7).

Recently, functional neuroimaging techniques have also been used for the clinical lateralization and localization of seizure foci. With the use of quantitative methods, fludeoxyglucose F 18 (FDG) positron emission tomography (PET) has been shown to lateralize correctly areas of hypometabolism that correspond to seizure foci in 52% to 85% of patients with temporal lobe epilepsy, and it has been suggested that qualitative PET scanning may have a role in this setting (8–11). Interictal single-photon emission computed tomography (SPECT) has also been reported to be useful for lateralization

TABLE 1: Clinical, EEG, and imaging characteristics for exculded patients

Patient	Age, y/ Sex	Outcome (Engel Class)	Findings at Invasive EEG Lateralization	Final Lateralization	QPET Lateralization	QMR Lateralization	PDH Lateralization	HV MR Lateralization	Disease
1E	30/M	I	. . .	LT	LT	LT	−0.005	NL	LT temporal dysembryoplastic neuroepithelioma
2E	38/M	II	BT: R > 90% L < 10%	RT	NL	NL	0.104	LT	RT mesial temporal sclerosis
3E	43/F	I	. . .	LT	LT	LT	0.004	NL	LT uncal ganglioglioma
4E	24/M	I	8 events in RT 2 events in LT	RT	RT	NL	−0.067	RT	RT hippocampal gliosis
5E	43/F	III	6 events in LT 1 event in RT	RT	RT	NL	−0.009	NL	None

Note—QPET indicates quantitative position emission tomography; QMR, qualitative MR imaging; PDH, percentage of difference among hippocampi; HV MR, quantitative MR imaging with hippocampal formation volumetric assessment; NL, nonlateralizing; RT, right temporal lobe; LT, left temporal lobe; and BT, bilateral tempora.

of the seizure focus interictally in 45% to 75% of patients with temporal lobe seizures (12, 13).

Qualitative visual analysis of magnetic resonance (MR) imaging studies (QMR) has been shown to lateralize areas of hippocampal atrophy correctly in 12% to 88% of patients with temporal lobe epilepsy (14–19). More recently, MR imaging techniques for accurate measurement of hippocampal volume (HV MR) have been shown to lateralize correctly areas of structural abnormalities in the temporal lobes that correlate with the side of seizure foci in 75% to 90% of patients with temporal lobe seizures (20–23). The purpose of this clinical study was to compare QPET, QMR, and HV MR in a series of patients with temporal lobe epilepsy for lateralization of seizure focus in the clinical setting.

Subjects and Methods

Patient Population and Selection Criteria

Twenty-one consecutive patients with temporal lobe epilepsy undergoing presurgical examination at the University of Florida's Shands Hospital had QPET, QMR, and HV MR examinations as described below.

All patients underwent anterior temporal lobectomy after examination, and a subgroup of these patients underwent invasive monitoring. Correct lateralization and localization were proved by Engel class I or II outcome at 1-year follow-up according to the system proposed by Engel (24), in which patients are assigned to one of four classes with each class having two to four subclasses, as outlined below.

Class I—seizure-free: completely free of seizures; auras only; some postoperative seizures, but otherwise seizure-free for more than 2 years; atypical seizures only during drug withdrawal.

Class II—rare seizures (no more than two per year): initially seizure-free, now rare seizures; rare seizures since surgery; rare seizures for more than 2 years, but now more than rare seizures; nocturnal seizures only with no associated disability.

Class III—"worthwhile" improvement (90% reduction): ongoing worthwhile reduction; worthwhile seizure reduction only within the past 2 years.

Class IV—no worthwhile improvement: some seizure reduction (more than 50% but less than 90%); no appreciable change (less than 50%); worsening seizures.

We excluded two patients with foreign tissue lesions (lesions other than mesial temporal sclerosis visible on QMR; ie, tumor, neoplasm). Three patients with bitemporal independent seizure foci identified by invasive monitoring were also excluded. Clinical data for these patients are presented in Table 1.

The group consisted of 10 male and six female subjects with a mean age of 30 years (range, 14 to 45 years). The mean duration of seizures in the 16 patients was 19 years (range, 6 to 41 years). Clinical features that were evaluated include age of onset of seizure disorder, seizure frequency, and presence/absence of previous febrile seizures. The seizure frequency was estimated by the physician obtaining the history immediately before video EEG monitoring. Age at onset was obtained by the physician taking the history and verified by outside records. These data are summarized in Table 2.

Focus/Epileptogenic Zone Determination

Interictal and ictal EEG data were recorded on a 64-channel/BMSI 4000 unit (Los Gatos, Calif) and reformatted to 64 channels in both referential and differential montages. All studies were reviewed by at least two board-certified (American Board of Clinical Neurophysiology) electroencephalographers. Assessment of site and of lateralization of the focus and epileptogenic zone was made on the basis of convergence of data derived from extracra-

TABLE 2: Characteristics of 16 patients with intractable temporal lobe epilepsy

Patient	Age, y/ Sex	Seizure Frequency	History of Febrile Seizures?	Duration of Seizures, y	Age at Onset, y
1	30/M	10 /mo	Unknown	29	1
2	30/M	10 /mo	Yes	27	3
3	45/F	3 /mo	No	35	10
4	18/F	3 /d	No	7	11
5	37/M	6 /mo	Yes	25	18
6	28/F	4.5 /wk	No	18	10
7	24/F	2 /wk	No	18	6
8	14/M	3 /d	Yes	6	8
9	36/F	3 /wk	Yes	35	1
10	45/M	10 /mo	Yes	37	8
11	45/M	5 /mo	No	8	37
12	30/M	1 /d	No	10	20
13	35/M	5 /wk	No	33	20
14	18/M	3 /mo	Yes	17	1
15	42/F	5 /wk	No	41	1
16	33/M	2 /d	No	20	1

nial (scalp/sphenoidal) EEG data, Wada testing data, neuropsychological data, QMR data, interictal SPECT data, and QPET data, but not HV MR data. In selected patients, invasive EEG data (from depth, grid, strip, and foramen ovale electrodes) were sought because of nonconvergent presurgical data. Indications for invasive evaluation were based exclusively on clinical situations, with electrode placement determined by issues specific to each patient.

PET Protocol

PET imaging was performed with a fixed multi-crystal 8192-element two-ring imager using coincidence-counting technology (ECAT 951: CTI Knoxville, Tenn, distributed by Siemens Medical Systems, Iselin, NJ) (C. O. Hendry, M. G. Straatmann, L. R. Carroll, et al, *Design and Performance of a Compact Radioisotope Delivery System,* Des Plaines, Ill: Siemens Gamma Sonics, Inc, Ord A 1004-M2330-T0030–01–4A00). The reconstructed z-axis resolution was 6 to 8 mm full width half the maximal (FWHM), the x-y resolution was 5 to 7 mm FWHM. Each acquisition covered a 10.3-cm axial field of view, with positioning to extend superior from the inferior cortices of the temporal lobes parallel to the canthomeatal line. In most adults, this field omitted 1 to 2 cm of the most superior transaxial planes; occasionally, an addition acquisition was required to include omitted cortex. Most images were reconstructed with a calculated attenuation-correction model. In some early cases, measured attenuation corrections were applied by using a preliminary transmission acquisition with a germanium-68 ring source and a plastic head-holder with laser position indicators.

Transaxial images were reconstructed for display in 3.3- and 9.9-mm contiguous image planes; coronal images perpendicular to the canthomeatal plane were reconstructed in 9.9-mm planes; sagittal images were also routinely included. Images were recorded from a digital display as transparencies with a monochrome gray scale for visual interpretation, adjusted so that image noise in the regions outside the head was just detectable without background subtractions, and differences in the brightest image pixels appeared just discernable without blocked regions.

F 18 was produced by using an 11-MeV negative hydrogen ion cyclotron (Radioisotope Delivery System, CTI Inc, Knoxville, Tenn; distributed by Siemens Medical Systems, Iselin, NJ) (19). Production of FDG was by a computer-controlled radiochemical synthesis (25). Radiopharmaceutical compounding was provided on site by Malinckrodt Nuclear Medicine (Tampa, Fla).

Chemical identify, purity, and safety analysis were routinely carried out on each preparation according to current US Pharmacopoeia standards. No adverse effects of the tracer material were noted in any patient. All patients fasted at least 4 hours before undergoing PET. Approximately 5 to 15 mCi FDG (dose was based on patient's weight) was injected while the patient was in a moderately darkened room, with minimal noise and distraction, and with eyes open. Within the standard dose range, additional doses (if available from the production yield) were administered in patients who seemed likely to have greater difficulty holding still. This technique shortened the imaging phase, allowing sufficient information to be acquired while the patient was motionless. All antiepileptic drugs were continued on the day of the study. EEG monitoring with scalp electrodes was carried out before and for at least 30 minutes after FDG administration. Imaging was initiated about 40 ($\pm$ 10) minutes after FDG administration. Patients were observed for any clinical manifestations of seizures before and during the procedure. When patients made voluntary movements after FDG injection, they were encouraged to remain quiet. When movement occurred during imaging, patients were repositioned with laser index assistance and acquisition was resumed. All PET scans were interpreted prospectively by one investigator by means of visual analysis. This investigator was blinded to all pertinent clinical data. This scanning technique represented the state of the art at the time the scans were performed (9–11).

MR Protocol

All studies were performed on a 1.0-T scanner with the following parameters: standard T1-weighted (500/15 [repetition time/echo time]) and T2-weighted (2500/20–80) sequences were obtained in the axial plane after a T1 localizing sequence was obtained in the sagittal plane; standard T1-weighted (500/15) sequences were obtained in the sagittal plane; and three-dimensional gradient echo volumetric sequences were obtained. The gradient-echo images were then transferred to an imaging processing laboratory for postacquisition processing, but they were not used for visual analysis. The parameters for the 3-D gradient-echo sequences included a magnetization-

Sagittal MR images through hippocampi: number at bottom right denotes area (plus or minus values indicate left or right of midline, respectively). Left and right hippocampal volumes are 1.78 cm^3 and 3.04 cm^3, respectively.
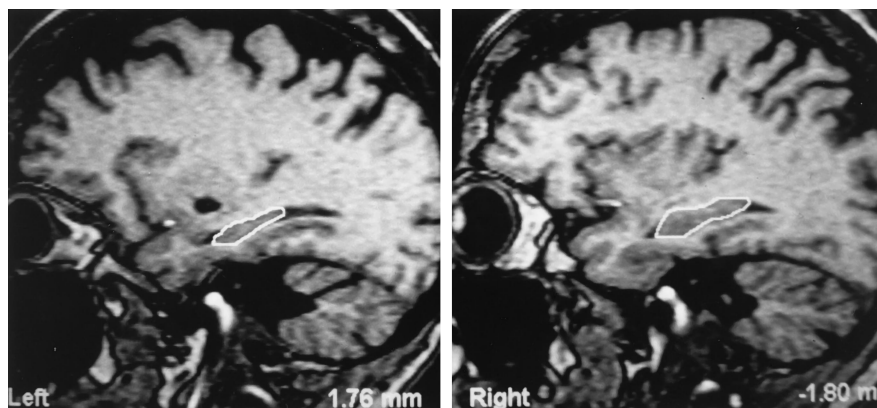
prepared rapid gradient echo (MP-RAGE) sequence obtained in the sagittal plane, 10/4, 250-mm field of view, 10° flip angle, 190 × 256 matrix, and 180-mm slab with 128 partitions producing 1.25-mm gapless sections. The MP-RAGE sequence provided a gapless series of high-contrast images of the whole brain, which were reconstructed into the sagittal plane. Sagittal images were used to minimize the difficulty in separating the amygdala from the hippocampus, because the alveus seen as a white band in sagittal sections between the amygdala and hippocampus serves as a border between the two structures. These images were then transferred electronically to a computer workstation. The standard QMR images were interpreted prospectively by one investigator who was blinded to all relevant clinical data. Hippocampal sclerosis was diagnosed if increased T2-weighted signal, decreased T1-weighted signal, or visually identifiable hippocampal asymmetry was present on QMR images. Asymmetry of the inferior horn of the lateral ventricle was not considered to be representative of hippocampal sclerosis.

Determination of Volumes

The hippocampal areas were measured by an examiner who was blinded to the patients' names, clinical data, and any other relevant data. In these 3-D sagittal gradient-echo volumetric sections the hippocampus is first visible medially in the anterior portion of the inferior horn of the lateral ventricle. The hippocampal formation was outlined manually by one of two investigators on every section where it appeared using programs in PC Wave (Visual Numerics, Boulder, Colo). The issue of interrater variability with this method was discussed in a previous publication by Gilmore et al (26). An example of the area determination on a single section is seen in the Figure. A typical hippocampus appeared in 15 sections. The section area was multiplied by section thickness to arrive at a hippocampal formation section volume. All section volumes were added to the other ipsilateral sections to arrive at a hippocampal volume. The volume of the left hippocampal formation was subtracted from the volume of the right hippocampal formation to determine a right-left asymmetry index, called the *difference in hippocampal formation*, similar to

that used by Jack et al (21). A ratio of difference in hippocampal formation to the sum of the right and left hippocampal formation volume was calculated, thus precluding the need for total intracranial volume normalization. This ratio is the percentage of difference in hippocampi (PDH).

In this study the patient was determined to have a right temporal lobe focus by HV MR when the PDH fell more than 3 standard deviations (SD) below the mean for healthy patients (less than −0.011). If a patient's PDH fell more than 3 SD above the mean (greater than or equal to 0.023), the patient was determined to have a left temporal lobe focus by HV MR. The PDH is similar to the hippocampal ratio discussed by Spencer et al (22). Validation of this method of determining hippocampal volume, difference in hippocampal formation, PDH, and interrater variability is discussed in detail by Gilmore et al (26). Statistical analysis between patients with lateralizing QPET, QMR, and HV MR studies and patients with nonlateralizing or incorrectly lateralizing studies was performed using Student's *t* test. The relationship between PDH and outcome class was explored by converting each patient's PDH into a *z* score by the use of mean PDH values and SD, as previously reported by Gilmore et al (26). The *z* scores were then used in Student's *t* test to compare outcome classes I and II. A similar method was used to compare PDH values in patients with and without a history of febrile seizures. Sensitivity was calculated as the number of patients with correctly lateralizing studies divided by the number of patients with correctly lateralizing studies added to the number of patients with incorrectly lateralizing or nonlateralizing studies.

Table 3 shows the patients' outcome class, scalp EEG location implanted, electrode locations, final EEG location, PET lateralization, PDH, HV MR lateralization, and QMR lateralization.

Results

Among the 16 patients, QPET was correctly lateralizing in nine patients (56%), nonlateralizing in six patients (37%), and incorrectly later-

TABLE 3: Outcome, EEG, and imaging data for 16 patients with intractable temporal lobe epilepsy

Patient	Outcome (Engel Class)	Scalp EEG Lateralization	Implanted Electrodes and Location	Final Localization	QPET Lateralization	QMR Lateralization	PDH	HV MR Lateralization
1	I	NL	B depths	RT	RT	RT	−0.177	RT
2	I	RT	R Grid/Str	RT	NL	RT	−0.244	RT
3	II	NL	B depths	RT	NL	NL	−0.022	RT
4	I	LT	Lat Grid/Str	LT	LT	RT	0.135	LT
5	I	NL	B depths	RT	ET	ET	−0.094	RT
6	I	LT	Lat Grid/Str	LT	LT	NL	0.212	LT
7	I	LT	Lat Grid	LT	NL	NL	0.123	LT
8	I	RT	None	RT	RT	NL	−0.239	RT
9	II	LT	None	LT	LT	NL	0.168	LT
10	I	NL	B Grid	LT	LT	LT	0.238	LT
11	I	RT	None	RT	NL	RT	−0.176	RT
12	I	LT	None	LT	NL	LT	0.215	LT
13	I	RT	R Grid	RT	RT	ET	−0.106	RT
14	I	RT	None	RT	RT	ET	−0.138	RT
15	II	RT	R Grid	RT	RT	NL	−0.205	RT
16	I	LT	Lat Grid/Str	LT	NL	LT	0.096	LT

Note—NL indicates nonlateralizing; Lat, lateralizing; B, bilateral; Grid, grid electrode; Str, strips; RT, right temporal lobe; LT, left temporal lobe; and ET, extratemporal.

alizing in one patient (6%). QMR was lateralizing in six patients (37.5%), nonlateralizing in six patients (37.5%), and incorrectly lateralizing in four patients (25%). HV MR was correctly lateralizing in all 16 patients (100%). In one patient, seizure focus was incorrectly lateralized with both QPET and QMR, but was correctly lateralized with HV MR. Comparison of the group of patients in whom QPET, QMR, and HV MR were correctly lateralizing with the group in whom these techniques were nonlateralizing and incorrectly lateralizing showed no statistical differences with respect to age of onset, total number of seizures, or duration of seizures ($P > .05$), although the statistical power of the study was limited owing to the small number of patients. Comparison of PDH in patients with class I and class II outcomes showed no statistically significant differences ($P > .05$). No difference was shown in PDH values between patients with and without febrile seizures. Sensitivity of QPET was 56%, QMR was 37.5%, and HV MR was 100%.

Discussion

In the surgical management of intractable temporal lobe epilepsy the question of lateralization of seizure focus frequently arises after scalp/sphenoidal video EEG monitoring yields equivocal results (5, 27, 28). This is a crucial issue for two reasons. The first reason is that correct lateralization is necessary for "good"

(Engel class I or II) outcome (see "Subjects and Methods" for definition of classes). The other reason correct lateralization of the seizure focus is critical is that a failure to lateralize the focus after a noninvasive examination may lead to additional surgery for placement of intracranial electrodes for lateralization or localization (1, 29). This additional procedure places the patient at risk for complications related to diagnostic surgery and incurs added costs.

Clinically, the additional information for lateralization gained via a noninvasive method allows this extra step in lateralization of temporal lobe foci to be bypassed, and thus avoids the above problems (30). Noninvasive studies of patients with temporal lobe epilepsy may be primarily structural or functional in nature, with structural techniques represented by MR imaging and functional techniques represented by PET and SPECT scanning. PET and SPECT scanning represent the two current methods of functional imaging in temporal lobe epilepsy. Several studies in which visual analysis has been used have demonstrated PET sensitivities of 80% to 85% in temporal lobe seizures, a rate that approaches the sensitivity found with the use of semiquantitative PET methods and approximately the rate seen in our study (8–10). QPET analysis is commonly used in the clinical setting (11). SPECT scanning in patients with temporal lobe epilepsy has also been correlated with seizure focus and with outcome after surgery for seizures (9, 12, 13, 31). The rate of

correct lateralization on interictal SPECT scanning has ranged from 45% to 75% (12, 13). Ictal SPECT scans have demonstrated higher rates of correct lateralization (32); however, in our institution (as in some others) these scans have proved difficult to obtain.

Early attempts at visual analysis of the medial temporal lobes on coronal, sagittal, and axial MR images generally showed that visual analysis alone had only modest sensitivity and specificity, although several investigators have reported a greater sensitivity and specificity (33–36). Jack et al (21), Spencer et al (22), and Cendes et al (36) developed methods for computerized volumetric analysis of the hippocampal formation on coronal sections that have shown excellent sensitivity, ranging from 75% to 92%, with specificities of 64% to 100% for temporal lobe seizure foci. These HV MR studies with coronal sections have been positively correlated with outcome data, pathologic material, and intracranial EEG recordings (37–39). Gilmore et al (26) reported a method of HV MR determination using sagittal sections that correlated HV MR asymmetry with seizure focus with a sensitivity of 88% and a specificity of 100% for temporal lobe epilepsy among patients with intractable seizures. A third and promising method of MR determination of temporal lobe seizure foci is that of quantitative MR T2 relaxometry described by Jackson et al (40, 41), which has been reported to have a sensitivity of 79% and a specificity of 100%. This method has also been correlated with EEG focus, mesial temporal sclerosis on pathologic examination, and surgical outcome (40, 41).

Our study shows that in this group of patients without obvious structural lesions, both QPET and HV MR are relatively sensitive techniques for the lateralization of temporal lobe epilepsy. QMR is relatively less sensitive in this group. We have subsequently begun including fast spin-echo sequences as part of our examination of patients with temporal lobe epilepsy. This method increases sensitivity and would have improved our QMR sensitivity (Browd SR, Gilmore R, Leonard CM, Quisling R, Roper SN, "Quantitative [MPRAGE of T2 Relaxation] and Qualitative [Fast Spin Echo] Analysis of Hippocampus in Complex Partial Epilepsy Using Magnetic Resonance Imaging [MRI]" *Epilepsia* 1994;35(suppl 8):21 [abstract]). Notably, the number of patients in our group was small, and larger numbers of patients may alter these re-

sults. However, in these patients, HV MR was able to lateralize seizure foci correctly in all the patients in whom foci were lateralized by PET. Clinically, this point is important because PET scanning is costly and may have limited availability, thus limiting its clinical use. MR imaging is generally available, and with some additional software, many centers could perform HV MR.

In our group of patients, eight of the 11 who underwent invasive monitoring would have been spared this procedure had HV MR data been used clinically as an aid in localization. This would have represented a significant savings to the patients in terms of surgical risk and cost. Another possible use of HV MR is in the identification of patients with bitemporal foci. Although this issue was not addressed in this study, active investigation in this area is ongoing at our institution.

In summary, our data for a select group of patients show that HV MR, QPET, and QMR yield data that may be clinically valuable in patients being considered for seizure surgery, but that HV MR yields considerably more information than QPET or QMR.

Acknowledgments

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