HIPDM-SPECT Brain Imaging in the Presurgical Evaluation of Patients with Intractable Seizures

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We report the results of interictal and ictal HIPDM-SPECT brain imaging in 34 patients who eventually underwent temporal lobectomy for treatment of medically intractable complex partial seizures. Interictal studies revealed decreased regional cerebral perfusion (rCP) in the temporal lobe corresponding to the eventual site of surgery in 73% of the patients. Similarly, ictal study demonstrated increased rCP in 93% of the patients. In 69% of the patients, the SPECT studies were able to demonstrate both increased rCP on the ictal scan and decreased rCP on the interictal scan in the same location, corresponding to the eventual site of surgery. These results suggest that interictal and ictal SPECT brain imaging can be easily obtained and provide reliable localizing information in the presurgical evaluation of patients with medically intractable epilepsy.

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In carefully selected patients with medically intractable complex partial seizures of temporal lobe origin, en bloc anterior temporal lobectomy is an established treatment option with beneficial results. One goal of presurgical evaluation in these patients is the accurate localization of the epileptogenic brain tissue responsible for the patient's habitual seizures. Clinical semiology of the seizure, focal electroencephalographic (EEG) slowing, interictal epileptiform abnormalities, ictal EEG patterns, computed tomography (CT) and magnetic resonance imaging (MRI) abnormalities, neuropsychologic dysfunction, and attenuation of thiopental-induced beta activity have all been employed to localize the area of seizure origin. The greater the concordance of these results, the greater is the confidence in localization of the seizure focus and recommending the appropriate surgical intervention (*1*). However, when sufficient supportive data are lacking or results of different tests are conflicting, further evaluation with invasive monitoring using stereotactically implanted depth or subdural grid electrodes is often required.

Major epilepsy centers have successfully utilized positron emission tomography (PET) with fluorine-18-fluorodeoxyglucose (FDG) to study patients with intractable epilepsy (*2,3,4*). The complementary result from interictal PET scan has allowed certain patients to bypass the need for invasive monitoring (*5*). Ictal FDG-PET studies have also been reported, but these are difficult to obtain and demonstrate variable results (*2,4,6*).

We undertook the investigation to determine if the more widely available single-photon emission computed tomography (SPECT) brain imaging would provide localizing information similar to that of PET scanning. We found SPECT brain imaging using N1N1N'-trimethyl-N'-(2 hydroxy-3-methyl-5-^{123}I-iodobenzyl)-1,3-propanediamine 2HCl (HIPDM) to be a reliable test in the presurgical evaluation of patients with medically intractable complex partial seizures. The results of the interictal and ictal HIPDM SPECT imaging in our series of patients who eventually had temporal lobectomy have been reported (*7*) and this is an extension of our previous work.

MATERIALS AND METHODS

Between September of 1984 and September of 1988, 34 patients at the Indiana University Medical Center underwent en bloc anterior temporal lobectomy for medically intractable complex partial seizure disorder. The patients were selected according to the criteria of the Indiana University Medical Center (Indianapolis) epilepsy surgery program protocol (*8*). These were patients who had medically refractory and socially disabling partial seizure disorder, with IQ greater than 70 and absence of psychosis. This report includes only patients who eventually had temporal lobectomy performed to allow assessment of surgical results and some indication of the appropriate localization of the epileptogenic focus.

Determination of Epileptic Focus

The patients underwent continuous video and EEG recording using the international 10-20 electrode placement system,

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sphenoidal electrodes implanted bilaterally, and 16 channel recording. In each patient, at least three habitual seizures were recorded. Location of the epileptic focus was derived from the combined results of the clinical semiology of the seizures, focal background abnormalities on the EEG (slowing), interictal epileptiform abnormalities, focal ictal EEG patterns, head CT scan, MRI scan, neuropsychometric testing, thiopental activation, Wada test, interictal HIPDM SPECT, and ictal HIPDM-SPECT (when available). Invasive monitoring with depth or subdural grid electrodes was not available at our institution during the study period.

Surgical Procedure

Standard en bloc anterior temporal lobectomy was performed on all the patients with additional limited frontal corticectomy in two patients (#10 and #24 in Table 1). Two other patients (#1 and #5) underwent a second operation when seizures recurred and MRI revealed significant residual hippocampus.

HIPDM-SPECT Brain Imaging

Details of the procedure of HIPDM-SPECT brain imaging have been reported previously (*7–10*). In brief, interictal scans were obtained on an outpatient basis while the patients were on their usual anticonvulsant regimen. High purity iodine-123 (Atomic Energy of Canada, Ltd.) was used to label the HIPDM and ~5 mCi dosage was given intravenously. In 16 patients, the interictal studies were repeated when the initial scan was nonrevealing, the first scan was technically poor, repeat studies using diamox were investigated, or patients were off all anticonvulsants during inpatient evaluation.

Scanning commenced 15-30 min after injection using a dual-headed camera (Siemens' Rota, Schomburg, IL) interfaced with a computer (Medical Data Systems A3, Ann Arbor, MI). Total scanning time was ~40 min. Transaxial, sagittal, coronal, and transverse (parallel to the orbitomeatal plane) images were obtained. A Butterworth filter at a proper cutoff was used. Attenuation corrections were not performed. The slices were 2-pixel or 12 mm thick. Spatial resolution was ~15x15x15mm.

The ictal scans were obtained as inpatient studies during the week of intensive video-EEG monitoring. Anticonvulsants had usually been tapered with the last dose taken on the day of admission. From Monday through Friday, the patients were transported to the EEG lab where they were monitored by video and EEG recording through the day. The patient and hardcopy of the EEG were continually monitored by an EEG technician situated at the bedside allowing HIPDM to be injected intravenously within one or two minutes of the onset of a seizure. The patient was transported to the nuclear medicine suite for scanning after injection.

Interpretation of the HIPDM-SPECT Scans

The interictal and ictal HIPDM-SPECT scans on the 34 patients were collected and presented to two nuclear medicine specialists (HP and AS). The interpreters were blinded to the clinical history but the scans were labeled as "interictal" or "ictal." The two physicians independently read the scans and recorded their interpretation. The criteria for identifying a region of the brain as abnormal was based upon qualitative differences in the regional cerebral perfusion. Where more than one interictal study was obtained and one scan was nonlocalizing, the result of the scan with a focal abnormality was tabulated as the overall result. There was a discrepancy between the readings in five patients and a final session was held involving two neurologists (WS and OM) who clarified any mistakes in labelling of the scans as "interictal" or "ictal." Ictal scans on patients who already had initial temporal lobectomy were also excluded from this study.

RESULTS

The patient population was comprised of 16 female and 18 male patients whose ages ranged from 8–42 yr (mean 28) and who had complex partial seizures intractable for 4–30 yr (mean 17) despite trials of 2–8 anticonvulsants (mean 4.7).

Head CT scan was abnormal in 6/31, but only 4/31 (13%) revealed focal abnormality localized to one frontal or temporal lobe. MRI scan was abnormal in 11/33 with only 9/33 (27%) demonstrating focal lesions. Neuropsychometric testing revealed bilateral dysfunction in 18/34 and lateralized dysfunction in 16/34 (47%). Erba-Lombroso (thiopental activation) test demonstrated lateralized attenuation of beta activity following intravenous sodium pentothal in 16/28 (57%). Pathology revealed an abnormality in 32/34 (94%) with gliosis present in 28/34 (82%); tumor, vascular malformation, or mild dysplasia in 7/34 (21%); heterotopia in 3/34 (9%); and inflammatory changes in 2/34 (6%) (Table 1).

Upon follow-up at 5 to 42 mo (mean 17.4 mo), 23/34 (67%) were free of complex partial seizures on medication; 6/34 (18%) had significant improvement in seizure control with >75% reduction in seizure frequency; 3/34 (9%) had no significant improvement; and two died (one due to malignant glioma and another due to an unrelated accident) (Table 1).

Interictal HIPDM-SPECT brain scans revealed decreased rCP in the right temporal region in 15/33, left temporal region in 10/33, and no significant abnormality in 8/33. In one patient (#15), the interictal HIPDM-SPECT was interpreted as decreased rCP in the left temporal region, but ultimately seizures were noted to arise from the right temporal region on ictal EEG and patient underwent right temporal lobectomy with good results. Overall, decreased rCP on the interictal HIPDM-SPECT scan was noted in the temporal lobe corresponding to the eventual site of surgery in 24/33 (73%) (Table 1).

Ictal HIPDM-SPECT brain scans revealed increased rCP in the right temporal region in 15/30, left temporal region in 13/30, bitemporal regions in one, and no localization in one. The ictal HIPDM-SPECT which revealed bitemporal uptake (Patient 15) was correlated with an ictal EEG demonstrating rhythmic activity beginning in the right temporal region and quickly followed by rhythmic activity in the left temporal region.

The ictal HIPDM study revealed focal increase of rCP in the epileptic foci even though the ictal onset in

TABLE 1
Results of Presurgical Evaluation and Surgery

No.	Name	Interictal EEG	Ictal EEG	Interictal SPECT	Ictal SPECT	Surgery	Pathology	Follow-up
1	RW	R Temp SW	R Temp	R Temp	R Temp	R Temp	Gliosis	SZ Free (Occ Aura)
2	JK	L Temp SW and Slow	L Temp-Fron	Normal	L Temp	L Temp-Fron	Gliosis	SZ Free
3	PH	L Temp SW and Slow	L Temp	Normal	L Temp	L Temp	Gliosis	2 SZ/3 mo
4	DF	L Temp SW	L Temp	L Temp	L Temp	L Temp	Gliosis	SZ Free (1 Aura/mo)
5	ST	L Temp SW	L Temp	L Temp	L Temp	L Temp	Gli/Vas. Mal.	SZ Free (Some Aura)
6	MG	L Temp SW and Slow	L Temp	L Temp	L Temp	L Temp	Gliosis	SZ Free
7	NH	R Temp SW and Slow	R Temp	R Temp-Par	R Temp	R Temp	Gliosis	2-4 SZ/mo
8	BM	R Temp SW and Slow	R Temp	Normal	Not done	R Temp	Normal	SZ Free
9	TK	R Temp SW and Slow	R Temp	R Temp	R Temp	R Temp	Glioma-Mix	SZ Free
10	JJ	R Temp and Bisyn SW	R Temp	R T-F-P	R Temp-Fron	R Temp	Gliosis	SZ Free
11	SG	R Temp SW and Slow	R Temp	Normal	R Temp	R Temp	Gliosis	1 SZ/3 mo
12	AC	R Temp SW and Slow	R Temp	R Temp	R Temp-Par	R Temp	Gliosis	SZ Free (2 Aura/mo)
13	TK	R Temp SW and Slow	R Temp	R Temp	Not done	R Temp	Gl. Multifor.	Deceased
14	SC	L Temp and Bisyn SW	L Temp	L Temp	L Temp	L Temp	Gli + Dysplas.	SZ Free
15	RD	R Temp SW	R-L Temp*	L Temp†	Bi-Temp	R Temp	Gliosis	SZ Free
16	JB	L Temp SW and Slow	L Temp	Normal	L Temp	L Temp	Gli + Dysplas.	SZ Free
17	SW	R Temp SW and Slow	R Temp	R Temp	R Temp	R Temp	Gliosis	SZ Free
18	LR	R, L Temp and L Fron	R Temp	R Temp, L Fron	R Temp	R Temp	Normal	11-15 SZ/mo
19	CS	L Temp SW	L Temp	L T-F-P	L Temp	L Temp	Gliosis	12-16 SZ/mo
20	CH	R Temp SW and Slow	R Temp	R Temp	Negative	R Temp	Gliosis	SZ Free
21	TJ	R Temp and Bisyn SW	R Temp	Normal	R Temp	R Temp	Gliosis	2 SZ/yr
22	RB	L Temp SW	L Temp	L Temp	L Temp	L Temp	Heterotopia	Deceased (Accident)
23	RG	R Temp SW	R Temp	R Temp	Not done	R Temp	Gli + Inflam.	SZ Free
24	JM	R Temp-Fron SW	R Temp	R Temp-Fron	Not done	R Temp-Fron	Gliosis	1 SZ/yr (Occ Aura)
25	AH	R Temp SW	R Temp	R Temp	R Temp	R Temp	Gli + Heterot.	SZ Free
26	MB	L Temp SW	L Temp	L Temp	L Temp	L Temp	Gliosis	SZ Free
27	AB	L Temp SW and Slow	L Temp	L Temp	L Temp	L Temp	Gliosis	SZ Free
28	DT	L Temp SW and Slow	L Temp	L Temp	L Temp	L Temp	Gliosis	1 SZ/3 mo
29	RO	R Temp SW	R Temp	R Temp	R Temp	R Temp	Gli + Dysplas.	4 Noc SZ/6 mo
30	JW	R Temp SW and Slow	R Temp	Normal	R Temp	R Temp	Gliosis	SZ Free
31	GC	L Temp SW	L Temp	Not done	L Temp	L Temp	Gliosis	SZ Free
32	NM	R Temp SW and Slow	R Temp	R Temp	R Temp	R Temp	Ganglioglio.	SZ Free
33	KC	L Temp SW and Slow	L Temp	L Temp	L Temp	L Temp	Gli + Heterot.	SZ Free (? Aura/wk)
34	KG	R Temp SW and Slow	R Temp	Normal	R Temp	R Temp	Gliosis	SZ Free

* Rhythmic activity began in R temporal region quickly followed by rhythmic activity in L temporal region.
† Interictal HIPDM-SPECT scan technically poor.
Vas. Mal. = vascular malformation; Gli = gliosis; GL Multifor = glioblastoma multiforme; Heterot = heterotopia; Dysplas = dysplasia; and Inflam = minimal inflammatory changes.

the EEG was focal/regional, lateralized, or diffuse. This focal hyperperfusion on the ictal study was noted as well when the seizure was a secondarily generalized tonic-clonic seizure. Overall, ictal HIPDM scans revealed increased rCP in one temporal region corresponding to the eventual site of surgery in 28/30 (93%).

Four patients had only interictal scans performed while one patient had an ictal scan without an associated interictal study. Of the 29 patients who had both interictal and ictal studies, seven had abnormal localizing ictal scans when the interictal scans were interpreted as normal. In addition, 20 (69%) of the patients

showed decreased rCP in the interictal and increased rCP in the ictal scan in the same temporal lobe which was subsequently resected (Fig. 1).

DISCUSSION

Engel at University of California, Los Angeles (UCLA) has been able to combine interictal FDG-PET results with results of other noninvasive tests to allow one-third of his patients to bypass invasive monitoring (*5*). PET is not readily available at many centers and ictal studies have been difficult to obtain due to the requirement for 30–40 min of steady state condition for uptake of FDG by the brain. In recent years, ^{123}I-labeled amines have been developed which cross intact blood-brain barrier and are distributed in the brain proportional to the regional cerebral perfusion (rCP). Magistretti and Uren used ^{123}I-labeled iodoamphetamine (IMP) SPECT in patients with complex partial seizures and demonstrated increased rCP during a seizure and decreased rCP in the interictal state (*11*).

We utilized [^{123}I]HIPDM which has a half-life of ~13 hr. This allows us to have the agent available while waiting several hours for a spontaneous seizure. The uptake by brain is rapid with 73.6% of the peak brain activity attained within 2 min of injection (*12*). This is essential for ictal studies as seizures with its associated physiologic changes occur on the same time scale of minutes and the rapid uptake would avoid significant incorporation of the postictal phase. Peak brain activity is reached within 20 min of i.v. injection of the agent. After it is taken up by the brain, there is no redistribution of activity for an hour or more, allowing ample time for satisfactory brain imaging.

Interictal HIPDM-SPECT scans revealed decreased rCP in the temporal lobe corresponding to the eventual site of surgery in 73% of our patients. This yield is similar to the results obtained with interictal PET scanning. In one patient, the decreased rCP was noted in the temporal lobe contralateral to the seizure focus documented by ictal EEG and therapeutic response (becoming seizure free) to surgery. Upon review, this study was noted to be technically poor in quality. The interictal SPECT result would also not be an inconsistent finding in a patient with bitemporal disease. This reaffirms the concept that a defect noted on interictal nuclear medicine scan does not necessarily imply the lesion is also epileptogenic. There is another possible cause of this discrepancy. Increased, as well as decreased, regional blood flow in the presumed seizure focus during the interictal state has been reported in literature (*13,14*) suggesting that regional CBF in the epileptogenic temporal lobe is not constant.

Reports from epilepsy surgery centers utilizing SPECT technology have concentrated on interictal studies in various patient populations with partial seizure disorder. The yield of abnormal interictal studies range from 57% to 86% (*11,14,16–18*). Associated ictal studies were not routinely performed or mentioned in these reports. The success of our current protocol indicates that it is logistically not difficult to obtain good ictal SPECT studies; we were successful in 30/34 (88%) of our patients.

Our results suggest that ictal HIPDM-SPECT can be a reliable diagnostic tool in the evaluation process of patients with intractable focal epilepsy. Increased rCP in the temporal lobe corresponding to the eventual site of surgery was present in 93% of the ictal studies. In no patient did the results conflict with the eventual site of surgery. The interictal and ictal studies are not redundant, but complementary. Some patients had normal or non-localizing interictal scans, but a localizing ictal study. The converse was also true. An area of decreased rCP on the interictal study represents a zone of dysfunction which may not necessarily be epileptogenic. However, concomitant increased rCP on the ictal study in the same region not only provides additional support for localization but also strong evidence for the epileptic nature of the lesion. When interictal EEG abnormali-

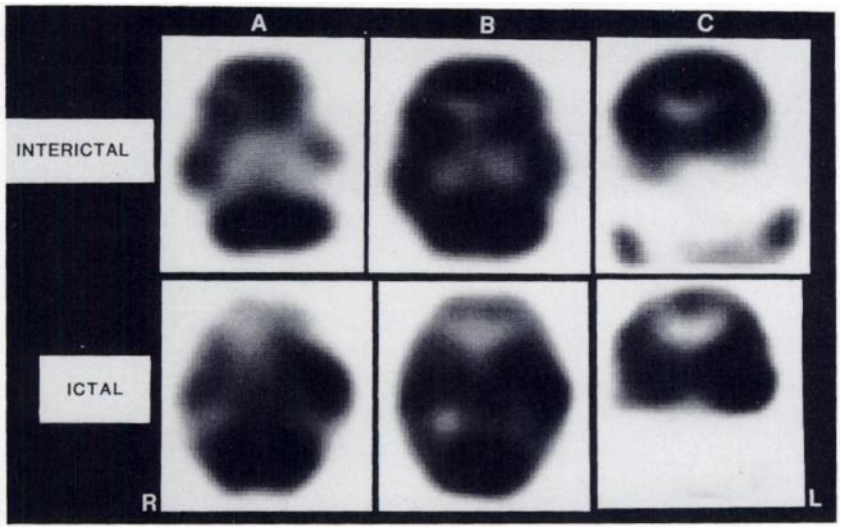

FIGURE 1
HIPDM-SPECT scans are shown with transaxial sections 24 mm (A) and 36 mm (B) above the orbitomeatal plane and coronal section through anterior temporal region. Interictal scan was interpreted as decreased rCP in the left frontotemporal region with ictal scan demonstrating hyperperfusion in the same location.

ties, ictal EEG patterns, interictal SPECT hypoperfusion, and ictal SPECT hyperperfusion all converge upon the same temporal lobe, one might conjecture that these results provide sufficient confidence to recommend temporal lobectomy and to bypass the risks associated with invasive monitoring utilizing subdural or depth electrodes.

There are some shortcomings to SPECT imaging in epilepsy. First, our preliminary experience suggests that HIPDM-SPECT brain imaging may not be as helpful with seizures of extra-temporal origin and when destructive structural lesions are noted on CT or MRI imaging. Second, SPECT studies may show rCP abnormalities not only in the temporal region but also in nearby frontal and parietal areas. Thus, localization of the seizure focus may not always be precise. Third, a positive interictal or ictal SPECT study does not rule out the possibility that the patient may have additional seizures arising from the contralateral temporal lobe. Fourth, the ictal SPECT could conceivably be positive in cases where ictal origin was remote from the area of increased uptake. Propagation of an ictal discharge into the temporal lobe could conceivably produce a focal ictal SPECT abnormality in the temporal region.

Conceptually, ictal EEG and ictal SPECT study results are complementary since they measure different physiologic parameters. However, further studies are required to document whether the results of SPECT and EEG are independent variables with respect to surgical outcome.

In our series, some patients had repeat interictal studies when the first scan was non-localizing. Since the localizing study was tabulated as the overall result, the 73% positive yield of our interictal studies may be an overly generous estimate. Future research should also address whether repeat ictal studies demonstrate consistent findings.

Presently, identification of an abnormal brain region on the SPECT image in epilepsy is qualitative, dependent on comparison of relative differences in regional cerebral perfusion and requires knowledge of whether the scans were ictal or interictal. Semiquantitative SPECT analysis may help to provide objective criteria for interpretation of the SPECT studies. This improvement in technology is being pursued at our institution.

In summary, when results of EEG, HIPDM-SPECT brain imaging, and other ancillary investigations all converge on the same temporal lobe, the findings may provide sufficient confidence to recommend temporal lobectomy without subjecting the patients to further invasive monitoring with its associated risks.

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