Does Performing Image Registration and Subtraction in Ictal Brain SPECT Help Localize Neocortical Seizures?

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Ictal brain SPECT (IS) findings in neocortical epilepsy (patients without mesiotemporal sclerosis) can be subtle. This study is aimed at assessing how the seizure focus identification was improved by the inclusion of individual IS and interictal brain SPECT (ITS)–MRI image registration as well as performing IS − ITS image subtraction. **Methods:** The study involved the posthoc analysis of 64 IS scans using ^{99m}Tc–ethyl cysteinate dimer that were obtained in 38 patients without mesiotemporal sclerosis but with or without other abnormalities on MRI. Radiotracer injection occurred during video-electroencephalographic (EEG) monitoring. Patients were injected 2–80 s (median time, 13 s) after clinical or EEG seizure onset. All patients had sufficient follow-up to correlate findings with the SPECT results. All patients had ITS and MRI, including a coronal volume sequence used for registration. Image registration (IS and ITS to MRI) was performed using automated software. After normalization, IS − ITS subtraction was performed. The IS, ITS, and subtraction studies were read by 2 experienced observers who were unaware of the clinical data and who assessed the presence and localization of an identifiable seizure focus before and after image registration and subtraction. Correlation was made with video-EEG (surface and invasive) and clinical and surgical follow-up. **Results:** Probable or definite foci were identified in 38 (59%) studies in 33 (87%) patients. In 52% of the studies, the image registration aided localization, and in 58% the subtraction images contributed additional information. In 9%, the subtraction images confused the interpretation. In follow-up after surgery, intracranial EEG or video-EEG monitoring (or both) has confirmed close or reasonable localization in 28 (74%) patients. In 6 (16%) patients, SPECT indicated false seizure localization. **Conclusion:** Image registration and image subtraction improve the localization of neocortical seizure foci using IS, but close correlation with the original images is required. False localizations occur in a minority of patients.

Key Words: SPECT; epilepsy; image registration; ^{99m}Tc–ethyl cysteinate dimer

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Ictal brain SPECT (IS) has been shown to be a sensitive means of identifying seizure foci (*1–11*). Most of these studies have focused on mesiotemporal lobe epilepsy, with few, if any, studies of patients with neocortical epilepsy. Those studies that have included patients with neocortical epilepsy appear to confirm the usefulness of ictal SPECT. This is important because neocortical seizure origin is particularly difficult to localize clinically by seizure characterization or electroencephalography (EEG), and the patient may have multiple underlying abnormalities on MRI, some or all of which may relate to the seizure focus. Other patients have normal MRI studies. To improve the sensitivity of seizure focus identification, O'Brien et al. (*8,12*) at the Mayo Clinic, Spanaki et al. (*9*) and Zubal et al. (*10*) at Yale University have introduced image subtraction (ictal − interictal [ITS]) techniques. These studies have included both temporal and neocortical patients.

At Dartmouth-Hitchcock Medical Center, we have a vigorous epilepsy surgery program with a special interest in neocortical epilepsy. Since 1994, IS has been performed on most patients with known or suspected neocortical epilepsy who are being considered for surgery (as well as many patients with suspected mesiotemporal lobe epilepsy). All patients undergoing IS have also undergone an ITS study and 3-dimensional MRI as part of their routine presurgical evaluation. In all of these patients, we coregistered both SPECT studies to the patient's MRI, using an automated registration algorithm, and subtracted the ITS from the IS scan after normalization.

This was a retrospective study designed to evaluate the sensitivity and specificity of IS in neocortical epilepsy and to assess the additional contribution of image registration and subtraction in these patients. We hypothesized that SPECT–MRI co-registration and IS − ITS image subtraction would significantly improve the accuracy of seizure focus localization in patients with neocortical epilepsy.

MATERIALS AND METHODS

Patients and IS Injections

From April 1994 to April 1999, 74 seizure patients undergoing presurgical evaluation at Dartmouth-Hitchcock Medical Center underwent at least 1 IS brain study, at least 1 ITS study, and MRI, which included a 3-dimensional spoiled gradient echo (SPGR) coronal sequence. This included all patients with neocortical seizures in whom the focus had not been identified previously and any patients with temporal lobe epilepsy in whom lateralization was in doubt. These data were used as part of the clinical management of these patients. Approval from the institutional review board at Dartmouth-Hitchcock Medical Center was obtained to review patient medical records and to perform the image registration and subtraction.

Patients were entered into this study if the data were available for all 3 studies (IS, ITS, and MRI), if the tracer used was ^{99m}Tc–ethyl cysteinate dimer (ECD), and if a mesiotemporal focus was not identified during the evaluation period or on surgical pathologic examination. The IS injections were performed in the epilepsy-monitoring unit during the patient's inpatient noninvasive evaluation, which included video-EEG monitoring with surface EEG electrodes. On the days when IS was to be attempted (usually after antiseizure medication withdrawal and sometimes sleep deprivation), a shielded syringe containing 1110 mBq ^{99m}Tc-ECD was brought to the unit and kept by the patient's bedside. A trained staff member remained by the patient's bedside from 8 AM until 4 PM. This syringe was recalibrated in the nuclear medicine department every 2 h, resulting in an injected dose of 888–1110 MBq. Injection of radiotracer was commenced as rapidly as possible after seizure onset was detected by either clinical signs or EEG changes, whichever came first. The injection time was calculated later through review of the video-EEG recording by an epileptologist experienced in EEG interpretation. The time in seconds from seizure onset (clinical or EEG, whichever came first) to the midpoint of the injection was taken as the injection time in seconds.

SPECT Imaging

Patients were transferred to the nuclear medicine division for imaging after stabilization. All scans were acquired on a Prism 3000 3-head gamma camera (Picker International, Cleveland, OH) using high-resolution collimators. Four 7-min SPECT images (each, 60 steps of 7 s each using a 128 × 128 matrix) were acquired. The raw data files were summed before image processing, after confirming lack of patient movement. If movement occurred, files were omitted as appropriate (maximum of 2 omitted). All studies were reconstructed in a similar manner using a ramp filter, followed by a postprocessing low-pass filter (order 4 with a 0.26 cutoff). Images were reconstructed in 3 planes, with 1-pixel-thick (2.225 mm) coronal slices used for registration purposes. Several patients had 2 or more IS studies performed (to confirm findings, because of late injections or because of atypical seizures or multiple seizure types). The patient's ITS studies were obtained after injection on a different day, frequently as an outpatient. The acquisition and reconstruction parameters were identical.

MRI

The MRI studies were acquired on a Sigma 1.5-T magnet (General Electric Medical Systems, Milwaukee, WI). As part of the routine epilepsy protocol, a 3-dimensional SPGR sequence was obtained in the coronal plane (124 × 1.5 mm slices), and this was used for registration purposes.

Image Registration and Subtraction

The MRI data were exported from the scanner in the Digital Imaging and Communications in Medicine format, and the SPECT data were exported in the Prism image format. These files were transferred through the hospital network to a personal computer workstation within the radiology department. The data were displayed, registered, and subtracted using a Windows network (NT)-based software package, RVIEW, developed initially at United Medical and Dental Schools Guys Hospital, London, and further extended at Yale University. A fully automated, rigid-registration algorithm based on the multiresolution optimization of normalized mutual information (*13*) was used to bring each SPECT image into alignment with the patient's high-resolution, 3-dimensional MRI scan. The accuracy and robustness of this registration approach for a similar task of MRI–PET brain registration have been investigated in an independent study by West et al. (*14*). However, in this application, we also made use of an interactive contour-based display of SPECT tracer uptake on orthogonal MRI brain slices (*15,16*) to visually confirm acceptable spatial alignment before image subtraction.

After spatial alignment, normalization of SPECT counts in the 2 images was then performed. A region of interest was manually placed within the midcerebellum region in the transaxial plane. A ratio of counts in the 2 SPECT scans in this region was used to estimate the global count ratio. We performed some initial trials with several different methods of image normalization and found, with the software we had available at the time, that the cerebellum produced the smallest inter- and intraobserver variability (A. Siegel and P. J. Lewis, unpublished data, December 1994). On rare occasions, contralateral cerebellar diaschisis may be seen in epilepsy. In these patients we used the normal (nonhyperperfused) hemisphere. A SPECT subtraction display was then produced in orthogonal planes using this normalization estimate.

Image Display and Interpretation

Images were retrospectively interpreted by the consensus opinion of 2 experienced nuclear medicine physicians, who were unaware of clinical information. Images were interpreted in the following sequence: First, the IS and ITS scans were viewed in all 3 orthogonal planes in an interwoven display. Scans were assessed for the presence and location of suspected seizure foci (hot spots). A consensus opinion between the 2 observers was used, and the interpretation was recorded. Second, the registered SPECT images were viewed with the MRI in orthogonal planes using a linked volumetric cursor with or without image overlay. Third, the registered and subtracted images were viewed in orthogonal planes. The subtracted images were displayed on a rainbow scale, and the window width was set so that background noise was just apparent. Registration was thought to have aided localization if it identified more clearly the location of a focus (e.g., parietal versus frontal lobe) or showed activity on the subtraction images to be extracranial. The subtraction images were thought to have aided localization if they either increased or decreased the certainty of identification of an equivocal focus or showed new unsuspected foci. The subtraction images were believed to have confused focus identification if they did not reveal a focus about which we had previously been confident or showed an additional focus or foci, which could

not be confirmed by review of the corresponding, nonsubtracted SPECT data.

The final certainty of focus localization (after registration and subtraction) was graded using a 0–4 scale as follows: 0, normal study (unchanged from IS); 1, probably not localizing; 2, equivocal findings; 3, probably localizing; and 4, definitely localizing. For analysis, only studies with a grade 3 or 4 (probable or definite) certainty of seizure localization were correlated with clinical results. The quality of the registration or subtraction was assessed on a 3-point scale: 1, poor (uninterpretable); 2, suboptimal but interpretation possible; and 3, good. Only registrations with scores of 2 or 3 were used for this study. All data were entered into an Access 97 (Microsoft, Seattle, WA) database at the time of image interpretation

Clinical Data

Clinical data were obtained on all patients after the retrospective image interpretation by observers who were unaware of the clinical findings. Data were obtained from the hospital chart and from the neurologists concerned with care of the patients. Demographic data and the history pertaining to each patient's seizures were obtained. The results of routine surface EEG, video-EEG monitoring, and invasive EEG monitoring (including sites of electrode placement) were recorded along with the type and date of any surgical procedures. The outcome of surgery was assessed using Engel's classification (*17*) (class 1, seizure free; class 2, rare seizures; class 3, little improvement; and class 4, no improvement) on the latest hospital visit at the time of analysis. The final seizure focus was identified from these data, where possible. Ideally, the gold standard was a successful surgical outcome, but because this occurred only in a proportion of the patients, other endpoints were believed to adequately confirm seizure foci. These endpoints were successful localization of a consistent focus by intracranial electrode monitoring or, in a few cases, scalp video-EEG monitoring of repeated stereotypic seizures recording a focus from the same site on every occasion. These latter cases were discussed individually with an epileptologist. Only those patients in whom adequate clinical or EEG data were present to identify the true seizure focus were used to correlate with the SPECT findings.

The SPECT focus localization was correlated with the clinical findings for each IS study using the following scale: close correlation, same area of same lobe; reasonable correlation, same lobe; nonlocalizing SPECT, focus not identified; and false localizing SPECT, focus in different lobe.

RESULTS

Demographics

Of the original 74 patients, 60 patients (28 female, 32 male) fulfilled the criteria for study entry for a total of 99 IS studies. Adequate clinical confirmation of the seizure focus was obtained in 38 patients with a total of 64 IS and 44 ITS studies. In the remaining 22 patients, it was believed that insufficient data were available for correlation with the SPECT scan (i.e., the true seizure focus could not be defined). This was associated with a multifocality of the seizures, lack of identification of a seizure focus by intracranial EEG, and surgery or intracranial monitoring not yet performed or insufficient follow-up (<6 mo) after surgery. Only those 38 patients (17 female, 21 male; mean age, 31 ± 10.9 y [mean ± SD]; age range, 9–59 y) with clinical confirmation of the seizure focus are described here. Patients underwent between 1 and 7 IS studies (median, 1 study/patient; mean, 1.7 studies/patient).

TABLE 1
MRI Findings in 38 Patients with Adequate Clinical Confirmation of Seizure Focus

MRI finding	No. of patients
Normal	13
Postsurgical changes	6
Single focal abnormality*	10
Multifocal abnormalities	3
Diffuse hemispheric abnormality	5
Bilateral diffuse abnormality	1

*Tumor, n = 5; cortical dysplasia or heterotopia, n = 2; encephalomalacia, n = 2; abnormal signal FLAIR (fluid attenuated inversion recovery) sequence only, normal pathology, n = 1.

Imaging Findings

MRI scans were normal in 13 of 38 patients and abnormal in 25. The MRI findings are listed in Table 1. In 38 of 64 (59%) IS studies a definite or probable seizure focus (grade 3 or 4) was identified. This resulted in a definite or probable focus localization on the basis of the SPECT studies alone in 33 (87%) patients when all IS studies on the same patient were considered. In 37 of 64 (58%) SPECT studies the subtraction images were believed to have aided localization of the seizure focus; in 6 (9%) studies the subtraction images confused localization. This occurred when a focus identified previously on the nonsubtracted images was not seen on the subtraction images or when the subtraction images displayed a lot of noise, showing a focus or multiple apparent foci that could not be confirmed on the raw data. SPECT–MRI registration was believed to have improved focus localization in 33 (52%) of studies.

Clinical Correlation

The locations of the 38 patients' seizure foci using the defined criteria are listed in Table 2. Thirty-one of 38 (81%)

TABLE 2
Seizure Focus Localization in 38 Patients with Adequate Clinical Confirmation of Seizure Focus

Site	No. of patients
Frontal	20*
Frontoparietal	2
Parietal	4
Parieto-occipital	1
Occipital	1
Temporal neocortex	11*

*One patient had 2 separate foci identified, left temporal neocortex and left frontal.

TABLE 3
Correlation Between SPECT and Clinically Identified Seizure Focus

Parameter	Close	Reasonable	Close or reasonable	Nonlocalizing by SPECT	False localizing by SPECT
No. of patients	22 (58)	6 (16)	28 (74)	4 (11)	6 (16)
No. of studies	32 (50)	9 (14)	41 (64)	16 (25)	7 (11)

Values in parentheses are percentages.

of these patients underwent intracranial monitoring with subdural electrodes (grids, strips) with or without depth electrodes. Thirty-one of 38 (81%) patients underwent surgery. There was obviously overlap between these 2 groups, but not all patients who had intracranial monitoring underwent surgery and vice versa. Patients were followed-up for 3–66 mo after surgery (mean ± SD, 26.6 ± 16.4 mo). The only patient with a follow-up of <8 mo died of respiratory arrest 3 mo after surgery.

In 28 (74%) patients the IS focus identified by SPECT correlated closely or reasonably closely with the final identified focus. In 4 (11%) patients the SPECT study(s) did not identify a focus, and in 6 (16%) patients an incorrect focus was identified by SPECT (Table 3).

Injection Timing

Injection timing could be obtained on 60 (94%) studies. Two video-EEG recordings were lost, and 2 patients were injected during status epilepticus. Patients were injected (earliest seizure start either clinical [video] or EEG to midpoint of dose injection) 17.5 ± 13.6 s (mean ± SD) into the seizure (median, 13 s; range, 2–80 s). The injection bolus usually took 1–2 s to complete. No significant difference in injection times was found between patients with close or reasonable SPECT clinical correlations (mean, 19 ± 14 s), nonlocalizing SPECT studies (mean, 12.2 ± 7.4 s), and false localizing studies (mean, 16.3 ± 15.6 s). However, 3 of 40 (7.5%) injections that resulted in close or reasonable SPECT correlations were >35 s, whereas in 2 of 7 (29%) false localizing studies injections were >35 s (no patients with nonlocalizing studies were injected this late). However, this was not statistically significant ($P = 0.1$; χ^2 test).

False Localizing Studies

The details of the 6 patients with false localizing SPECT studies are shown in Table 4. Patient 33 had a very subtle right temporal focus on SPECT (true left temporal focus) that, in retrospect, should have been ignored. We do not believe that this is a truly false localizing IS scan. One SPECT study performed on patient 35 after an isolated aura rather than during a seizure showed a right temporal focus, whereas an injection during a complete seizure revealed a left temporal focus. The patient was shown eventually to have a left occipital focus. Patient 62 had bitemporal foci on SPECT; the intensity was greatest in the left temporal lobe and this was named as the focus (true focus = right temporal lobe). Patient 62 had a late (48 s) injection after generalization, and patient 65 was injected during status epilepticus. In retrospect, there is no clear reason for the false localizations in patients 38 and 64 or for the second injection in patient 35. These patients all had intense, unequivocal IS foci on review.

DISCUSSION

Surgical excision of the seizure focus is well established for the treatment of mesiotemporal lobe epilepsy, with three fourths of patients either being cured or having a significant improvement in seizure frequency after surgery (*18,19*). Neocortical epilepsy, epilepsy in which the seizures originate outside of the mesiotemporal lobe structures, is a more difficult surgical management problem. The cure rates for surgery are lower (*20,21*), and localization of the seizure focus or foci before surgery is considerably more complex. Up to 83% of patients with neocortical epilepsy in 1 series (*21*) have identifiable single anatomic abnormalities on MRI, such as tumors (benign or malignant); congenital malformations; or the remote effects of trauma and cerebrovascular accidents. In these patients, the success rate for surgery is relatively high (86% surgical benefit versus 60% in patients with no focal MRI abnormality) (*21*). In patients

TABLE 4
Details of Patients with False Localizing SPECT Studies (Not Within Same Lobe)

Patient no.	True localization site	SPECT localization site	Injection time (s)	Note
33	L temporal	R temporal	10	Probable overreading of SPECT study
35	L occipital	SPECT 1, R temporal	12	Aura injection
		SPECT 2, L temporal	12	
38	L frontoparietal	R orbitofrontal	8	
62	R temporal	L temporal	48	Bilateral temporal activation on SPECT, L > R
64	R temporal	L temporoparietal	8	
65	L frontal	L mediotemporal	?	Patient in status epilepticus

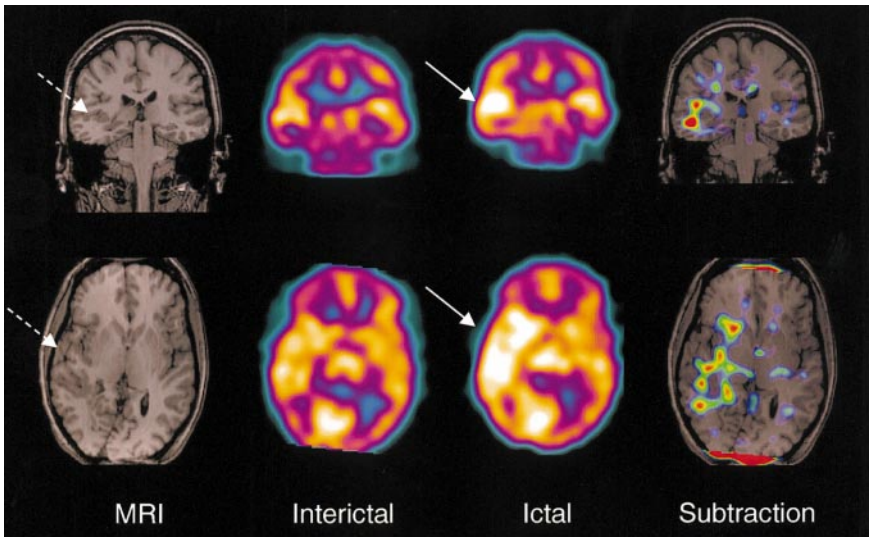

FIGURE 1. Example of benefits of image registration in 38-y-old woman with complex partial seizures. MRI shows right temporal heterotopia (dashed arrow). Axial IS and subtraction show right temporal hyperperfusion (solid arrow) and right basal ganglia hyperperfusion. Registered images confirm that former lies at site of extensive heterotopia. Seizure focus was confirmed on video-EEG recording. Surgery is planned.

with normal MRI scans, or MRI scans revealing multiple abnormalities, localization of the focus is difficult and usually requires 1 or more sessions of invasive electrode monitoring after noninvasive testing has identified the suspected general area of seizure origin. Nonconcordance between MRI and IS video-EEG has been reported in 3%–40% of patients (*20*). Not infrequently, at least at major epilepsy centers, these patients return for further surgery after a limited or unsuccessful resection.

Ictal SPECT scans using either ^{99m}Tc-hexamethylpropyleneamine oxime or ^{99m}Tc-ECD have been shown to be an accurate means of localization of temporal lobe seizures (*1–5,5–10,20,22–26*), with seizure localization reported in 86%–97% of patients. Incorrect localization is reported in 0%–6% of patients. Therefore, ictal SPECT has become a routine part of the management of patients with temporal lobe epilepsy in many centers, although the distinction between mesiotemporal and temporal neocortical epilepsy is usually not made by SPECT (*23*).

Unfortunately, the success of SPECT with neocortical seizures has been somewhat less. Few studies have concentrated solely on neocortical patients, with most studies containing mixed populations of patients with small numbers of neocortical patients. Neocortical seizure focus localization by IS appears to be somewhat less accurate, with reported sensitivities of 39%–100% of patients (*6,9,10,20,22,24,27–34*), with occasional false localizations (up to 11% but the numbers are very small (*24,34*)). A major difficulty with interpretation of all published IS data is the variability of the gold standard used to obtain sensitivity calculations. A recent meta-analysis by Devous et al. (*11*) concluded that, using their defined criteria, insufficient data existed to form conclusions regarding the usefulness of IS in neocortical epilepsy. The ultimate gold standard is surgical excision of a focus with the patient becoming seizure free. However, this standard is used only in a few of the studies. In several studies, correlation is made only with surface EEG recordings (*2–4,22,26,27,33,34*). In particular, because of the complexities of the extratemporal group, many patients do not undergo surgery. The problem is even worse when attempts are made to calculate specificity of IS because the true-negative is unknown—by definition, all patients have a seizure focus or foci. ''False localization rate'' is probably the better term used here.

An additional problem with neocortical epilepsy is the marked heterogeneity of this patient group, with many patients having either subtly or frankly abnormal (almost always in the presence of abnormal MRI scans) baseline cerebral perfusion studies. The abnormal baseline (ITS) study can make image interpretation difficult. The exact

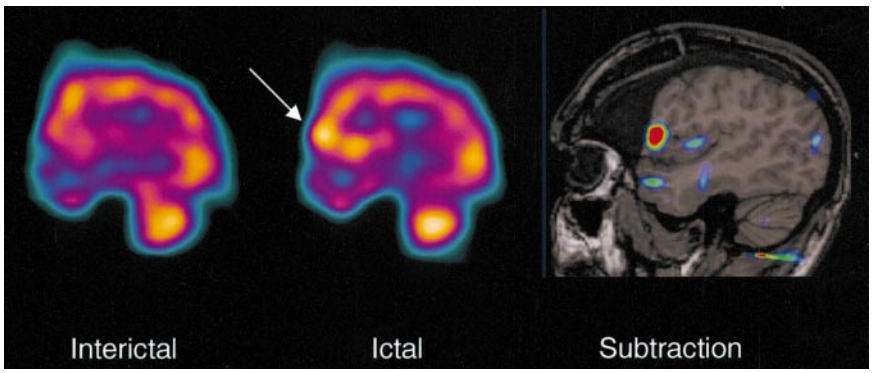

FIGURE 2. Example of benefits of subtracted registered images from 30-y-old man with recurrent seizures after right frontal resection. Very subtle IS focus that registers to posterior resection margin (arrow) on sagittal IS images shows much more obviously on subtraction images. This was confirmed by subdural electrodes. Further resection was performed, and patient is seizure free 38 mo after surgery.

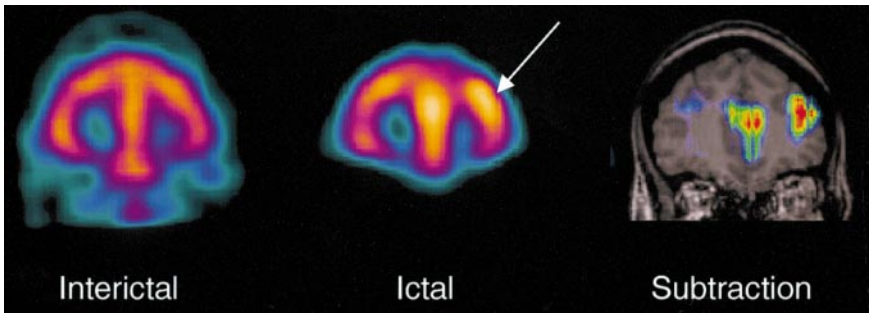

FIGURE 3. Example of benefits of image subtraction in 40-y-old woman with complex partial seizures. Left lateral frontal focus (arrow) was identified on original coronal SPECT images, but second left mesiofrontal focus was not recognized until subtraction images were viewed (registered data with linked cursors show "midline" focus to be to left of midline). Two separate foci (left mesiofrontal and lateral frontal) were confirmed by subdural electrodes.

localization of foci within the cerebral cortex (e.g., frontal versus parietal) can be challenging given the limited anatomic information on a conventional brain SPECT scan. Two adjuvant techniques that have been used are image coregistration between the SPECT and MRI scans to improve anatomic localization and subtraction of the ITS scan from the IS to improve sensitivity for lesion identification (*8–10*,*12*,*32*). These methods do appear to significantly improve IS accuracy, with localization rates increasing from 39% to 88% in the study by O'Brien et al. (*8*).

SPECT–MRI image registration is now commonplace and, with the development of fast, automated algorithms, can be performed routinely during clinical studies. The technique is relatively simple, allowing a physician or technologist to transfer data and perform image registration and subtraction in ~20 min on a personal computer. We no longer interpret IS scans without registered and subtracted images. Image registration has 2 major benefits: It allows image subtraction to be performed and it allows accurate anatomic localization of a suspected focus on both the raw data, particularly in patients with abnormal MRI scans, and the subtracted images, which contain no anatomic information (Fig. 1). In our study, registration contributed information in 52% of the studies. Our study also confirmed the results of others (*8–10*,*12*) in validating the usefulness of the subtraction images, contributing to 58% of study interpretations. In some patients with clear focal increases in cerebral perfusion on the raw IS data, the subtraction images added no additional information. In others, the subtraction images significantly increased or decreased our confidence in identifying a subtle focus or identified a new, unsuspected focus or foci. Because the subtraction images have the potential for producing significant artifacts, particularly if registration is suboptimal, we believe that they should be interpreted only in conjunction with the original data. In all cases, retrospective review of the original data, using linked volumetric cursors between all image sets, confirmed the presence of a focus initially seen only on the subtraction images (Figs. 2 and 3). This occurred frrequently in patients with a very subtle area of hypoperfusion on the ITS images, which normalized on the IS study without ever appearing as a frankly hyperperfused area. Others have also found that the magnitude of perfusion increases in neocortical epilepsy is less than that in mesiotemporal epilepsy (*29*) and therefore is more difficult to detect on the raw data. In many patients the area of relative hyperperfusion is considerably larger than what is eventually found to be the focus with depth electrodes. This has been found in many IS studies, including those in patients with mesiotemporal sclerosis, where typically both lateral and medial hyperperfusion is seen. We typically take the area of maximal hyperperfusion to be the focus.

We chose not to quantify our subtraction images because, after some preliminary experiments, we found that decreasing the top window level to a scale where background noise became visible provided the most useful information in these patients with highly variable degrees of seizure activation. Although this could potentially increase our false-positive rate (by reducing the scale too far), retrospective review of our false localizations found all but 1 to be in patients with the highest increases in focal perfusion (20%–30% above background; Fig. 4).

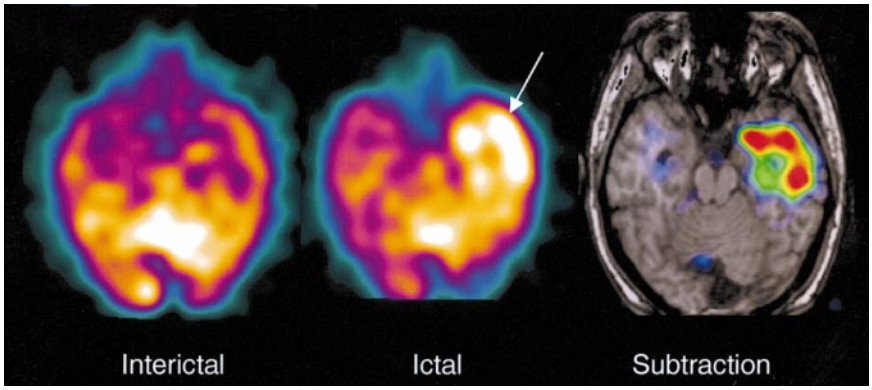

FIGURE 4. Example of false localization. Axial ITS, IS, and registered subtracted images in 32-y-old man with intractable seizures. MRI showed bilateral occipital heterotopia. IS (injection at 12 s) shows clear left temporal hyperperfusion (arrow), with normal occipital areas. Subdural grid placement revealed left inferior occipital focus. Surgical resection was performed, and 2 y after resection patient is Engel class 2.

Our localization rates were slightly less than those reported in some studies, identifying an IS focus in 87% of patients. Our correct localization rates (lobar or sublobar localization in 74% of patients) were also less than some reported. This finding may be associated with the patient group we studied: All patients had intractable neocortical seizures of highly varied etiologies. Many had been referred because of failure of localization elsewhere (e.g., usually not those patients with single clearly identifiable anatomic abnormalities on MRI), and 6 had undergone prior surgery that failed. We also used very strict criteria to allow adequate clinical correlation, which resulted in a large percentage (37%) of our patient population reaching entry criteria being excluded from the study. The false localization rate of 16% of patients (11% of IS studies) is worrisome. Two cases could be explained by late injections, 1 study was during an aura, 1 had bitemporal activation, and 1 had probable overinterpretation of the SPECT data. This still leaves 3 studies for which no reason could be identified for the false localization. One hypothesis is that the patients rapidly generalized or switched foci—this is a factor in many patients with neocortical seizures—or that the patient has multifocal seizures with different foci being identified by SPECT and intracranial EEG (*35*). Injections during isolated auras and rapid generalization have been blamed for false localizations in another study (*5*). The association of ipsilateral and even contralateral mesiotemporal hyperperfusion with occipital lobe seizures, as occurred in patient 35, has been reported (*30*) and is probably associated with occipital seizure propagation patterns. The clinical presentation of occipital seizures that shows a pattern of temporal lobe seizures on EEG is well recognized (*36*) (Fig. 4). Bilateral temporal hyperfusion from unilateral temporal neocortical foci has been described by Ho et al. (*23*) and is probably associated with anterior commissural connections between the lateral temporal cortex and the contralateral amygdala as occurred in 1 of our patients. Several studies (*8,37,38*) have shown that when the SPECT (or PET) and EEG localizations are discordant, the success rate of surgery is significantly lower: 62.5% for concordant versus 20% for nonconcordant localizations in 1 study (*8*). However, this does not fit with our experience because in the 5 of 6 patients with false SPECT localizations who have gone to surgery, all have had Engel class 1 or 2 outcomes. This underlines the fact that all seizure localization tests—EEG MRI, SPECT, or clinical evaluation—may produce false-positive results and that the patient must be managed using the combination of all of these tests rather than 1 individual test.

Our injection times are as good as or better than those in the published literature (*2,5,8–10,22–24,32,34*), with a median injection time of 13 s. These times are at the midpoint of the injection; many studies (when stated) use the start of the injection as the timing point. Rapid generalization and short seizure duration are significant problems with neocortical epilepsy. Transit of the radiotracer from the arm to the brain may take up to 25 s after injection, and late injections have been shown previously to be less accurate in determining the seizure focus (*25*). However, in our study we failed to identify a difference in mean injection timing between well-localized, nonlocalized, and falsely localized SPECT studies. This may be attributed to the very small number of significantly late injections (only 3 were $>$35 s plus 2 patients in status epilepticus). Interestingly, 29% of false localizations were $>$35 s compared with 7.5% of close or reasonably localized SPECT studies. However, this was not statistically significant. For these reasons, we believe that extremely early IS injections (preferably $<$20 s) are mandatory, and results must be carefully correlated with a knowledge of the injection timing (*39*) and EEG findings at the time of injection and the following 30 s. These short injection times require the constant attendance of a trained person at the patient's bedside, with particular attention to radiation safety. We place the syringe containing the radiotracer within a specially designed syringe shield attached to the patient's intravenous tubing at all times. A late injection usually resulted in a further study being performed.

Other investigators (*3,7*) have postulated the theory of the post-ictal switch in perfusion, in which the seizure focus is revealed as an area of relative hypoperfusion on post-ictal SPECT images. These studies (all involving temporal lobe epilepsy patients) have shown that this switch occurs at least 30 s and as long as 2 min after seizure completion. Our injections were all ictal, not post-ictal, and thus this switch should not have occurred, even accounting for circulation times. In addition, post-ictal SPECT studies have not been shown to be useful in neocortical epilepsy (*29,34*) when late injections may result in isoperfusion, hypoperfusion, or false localization. Therefore, in our study we did not assess for focal hypoperfusion by routinely performing ITS − IS subtractions (i.e., post-ictal–type changes). However, it is possible that incorporating this information into our future protocols would improve the sensitivity.

CONCLUSION

Ictal SPECT studies can be performed in patients with neocortical epilepsy, but these studies require considerable dedication from both the clinical and the nuclear medicine departments. They appear to be a helpful tool for the epilepsy team, particularly in the planning of subdural electrode placement, reducing the area of cortex that needs to be covered, and, hence, the morbidity. IS − ITS should be performed whenever localization by extracranial electrodes or MRI is equivocal. However, the data are too preliminary to be used for planning resections without intracranial electrode placement, except in those patients in whom a positive IS study confirms a focal MRI abnormality. Very early ictal injections are vital because of frequent rapid propagation of many neocortical seizures. All SPECT findings should be carefully correlated with the video-EEG data at the time of injection. SPECT–MRI registration and IS − ITS image subtraction add considerably to SPECT interpretation and can be performed rapidly. IS images should not be

interpreted in these patients without a baseline ITS study, and all subtraction findings should be compared with the raw data. False seizure localization does occur in a minority of patients, and if SPECT and EEG or clinical findings are discordant and particularly if the possibility of multifocal seizures exists, a further IS study should be considered.

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