Is ^{11}C -flumazenil PET superior to ^{18}F FDG PET and ^{123}I -iomazenil SPECT in presurgical evaluation of temporal lobe epilepsy?

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Abstract

Objective—To determine the contribution of ^{18}F FDG PET, ^{11}C -flumazenil PET, and ^{123}I -iomazenil SPECT to the presurgical evaluation of patients with medically intractable complex partial seizures.

Methods—Presurgical evaluation was performed in 23 patients, who were considered candidates for temporal lobe resective surgery (14 females and nine males with a median age of 34 (range 13 to 50) years). The presurgical diagnosis was based on seizure semiology as demonstrated with ictal video recording, ictal and interictal scalp EEG recordings, and MRI.

Results—Eighteen patients had convergent findings in clinical semiology, interictal and ictal EEG with scalp and sphenoidal electrodes, and MRI that warranted surgery without depth EEG (DEEG). In five patients with insufficient precision of localisation, DEEG with intracerebral and subdural electrodes was performed. MRI showed abnormalities in 22 out of 23 patients. Of these 22, 18 had mesial temporal sclerosis. This was limited to the mesial temporal lobe in four and more widespread in the temporal lobe in 14 patients. In one patient only enlargement of the temporal horn was found and in three others only white matter lesions were detected. ^{18}F FDG PET showed a large area of glucose hypometabolism in the epileptogenic temporal lobe, with an extension outside the temporal lobe in 10 of 23 patients. Only in one of these patients DEEG showed extratemporal abnormalities that were concordant with a significant extratemporal extension of hypometabolism in ^{18}F FDG PET. ^{18}F FDG PET was compared with the results of scalp EEG: in none of the patients was an anterior temporal ictal onset in scalp EEG related to a maximum hypometabolism in the mesial temporal area. By contrast, the region of abnormality indicated by ^{11}C -flumazenil PET was much more restricted, also when compared with DEEG findings. Extension of abnormality outside the lobe of surgery was seen in only two patients with ^{11}C -flumazenil and was less pronounced compared with the intratemporal abnormality. Both ^{18}F FDG PET and ^{11}C -flumazenil PET reliably indicated the epileptogenic temporal lobe. Thus these techniques provide valuable support for the presurgical diagnosis,

especially in patients with non-lesional MRI or non-lateralising or localising scalp EEG recordings. In those patients in whom phase 1 presurgical evaluation on the basis of classic methods does not allow a localisation of the epileptogenic area, PET studies may provide valuable information for the strategy of the implantation of intracranial electrodes for DEEG. Previous studies have suggested that ^{11}C -flumazenil binding has a closer spatial relationship with the zone of ictal onset than the area of glucose hypometabolism, but this study suggests rather that the decrease in the ^{11}C -flumazenil binding simply reflects a loss of neurons expressing the benzodiazepine-GABA receptor. ^{11}C -flumazenil PET did not prove to be superior to ^{18}F FDG PET.

Conclusion—In 21 patients sufficient material was obtained at surgery for a pathological examination. In 17 mesial temporal sclerosis, in one an oligodendroglioma grade B, in another a vascular malformation and in two patients no abnormalities were found. Although all 21 patients with pathological abnormality showed hypometabolic zones with ^{18}F FDG PET and a decreased uptake in ^{11}C -flumazenil binding, there was no strong correlation between pathological diagnosis and functional abnormal areas in PET. Grading of medial temporal sclerosis according to the Wyler criteria showed no correlation with the degree of hypometabolism in either ^{18}F FDG or ^{11}C -flumazenil PET.

The interictal ^{123}I -iomazenil SPECT technique was highly inaccurate in localising the lobe of surgery.

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Keywords: FDG PET; flumazenil PET; iomazenil SPECT; temporal epilepsy; epilepsy surgery

In patients with medically refractory epileptic seizures of temporal lobe origin who are candidates for epilepsy surgery, a careful presurgical evaluation is necessary for a precise definition of the zone of ictal onset. Diagnostic procedures should be limited both in number and in invasiveness. In the first investigative phase of the Dutch Epilepsy Surgery Programme, in accordance with international consensus, only non-invasive examinations are carried out.¹

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Table 1 Patients, history, and seizure type

Patient no	Sex	Age at seizure onset	Aetiology	Seizures	Age at surgery
1	F	3	None	CP	TC
2	M	6	None	SP	TC
3	M	8	Febr conv	CP	TC
4	F	19	None	CP	TC
5	F	1	Meningitis	SP	CP
6	F	9	Febr conv	SP	CP
7	F	14	None	SP	CP
8	M	6	Febr conv	SP	CP
9	F	3	None	SP	CP
10	M	1	None	SP	CP
11	M	20	None	CP	TC
12	M	7	Febr conv	SP	CP
13	F	7	None	CP	TC
14	M	5	None	SP	CP
15	F	7	None	SP	CP
16	F	4	Febr conv	SP	CP
17	M	12	None	SP	CP
18	F	21	None	SP	CP
19	F	5	Febr conv	SP	CP
20	M	12	Febr conv	SP	CP
21	F	12	Febr conv	SP	CP
22	F	4	Febr conv	SP	CP
23	F	18	None	SP	CP

SP = Simple partial seizures; CP = complex partial seizures; TC = generalised tonic-clonic seizures; febr conv = febrile convulsions.

At present in most patients a satisfactory precision of localisation can be obtained with the use of non-invasive techniques which comprise interictal and ictal EEG-CCTV monitoring with scalp and sphenoidal electrodes, CT, MRI, and neuropsychological examination. Consequently a decreasing number of patients require a second (invasive) phase of investigation comprising recordings with subdural and intracerebral EEG (DEEG) electrodes.²

In the programme special attention has been given to the contribution of ¹⁸FDG PET and ¹²³I-iomazenil SPECT.³⁻⁵ Recently ¹¹C-flumazenil PET was added to the phase 1 studies in the context of medical technology assessment.

It has been suggested that the area of reduced benzodiazepine (BZ) receptor binding in ¹¹C-flumazenil PET is smaller and correlates more closely with the clinical symptomatogenic zone and the EEG localisation than the area of

reduced cerebral metabolic rate of glucose (CMRGlu) in ¹⁸F-fluoro-deoxy-D-glucose (¹⁸FDG) PET.⁶⁻⁸ As comparative data on these two techniques are limited, it is not yet clear whether they are complementary⁹ or whether one technique yields superior results.

¹²³I-Iomazenil, a flumazenil derivative, is a radioligand for BZ receptors which can be used with SPECT.⁵ SPECT is less expensive and more widely available than PET.

Here we consider the question of whether, and to what extent, there is evidence of a contribution of ¹⁸FDG PET, ¹¹C-flumazenil PET, and ¹²³I-iomazenil SPECT to the presurgical evaluation in 23 patients with medically intractable complex partial seizures. The answer to this question will indicate which method could be considered redundant. This is important to prevent excessive radiation exposure.

Patients and methods

GENERAL CHARACTERISTICS

In 23 patients who were candidates for temporal lobe resective surgery because of epilepsy the relation between the results of the presurgical evaluation, outcome data, pathology, and functional neuroimaging examinations were compared. Tables 1-4 present the data.

The 23 patients (table 1), 14 females and nine males, had a median age of 34 (range 13 to 50) years. The presurgical diagnosis after the non-invasive phase 1 study was based on seizure semiology from ictal video recording, ictal and interictal scalp EEG recordings, and MRI. In the invasive part (phase 2) of the presurgical evaluation all patients had a sodium amobarbital test (Amytal® test). In five patients, in whom insufficient precision of localisation of the epileptogenic area was obtained, EEG with intracerebral and subdural

Table 2 Presurgical evaluation phase 1 and phase 2

Patient no	MRI				Localisation ictal EEG	Conclusion phase 1 functional diagnosis	Conclusion phase 2 DEEG conclusion	Lobe of surgery
	MTS	MTS criteria	Temp lesion no MTS	Extra temporal abnormality				
1					R frontotemp	R Frontotemp	Mesio/neocort temp	R temp
2	T	1,2	T		R temp	multifocal?, R temp?	Neocort temp	R temp
3	T	2,4			R front paramed	R Frontotemp	Mesio/neocort temp	R temp
4		5			R front/temp	R temp-front	Mesio/neocort temp, orb front	R temp, front
5	T	1,2			L posttemp	L temp: post	Mesio temp	L temp
6	T	1		W	R ant temp	R ant temp		R temp
7	T	1,2			R ant temp	R ant temp		R temp
8	T	1,2,5			R Frontotemp	R temp		R temp
9	T	1,2,4,5			R ant temp	R ant temp		R temp
10	T	1,2,4,5			R ant temp	R ant temp		R temp
11	T	1,2,3,4			no lat/loc	R temp		R temp
12	T	1,4,5			R ant temp	R ant temp		R temp
13	T	1,2,4			R ant temp	R ant temp		R temp
14	T	1,2,4,6			R temp	R temp		R temp
15	T	1,2,3,4,5			R ant temp	R ant temp		R temp
16	T	1,2,4,5,6			Lat R hemisphere	R temp		R temp
17		4,5			R temp	R temp		R temp
18				W	R ant temp	R ant temp		R temp
19	T	1,2,3,6			L temp	L temp		L temp
20	T	1,2,3,4,6			L ant temp	L temp		L temp
21	T	2,4			L ant temp	L ant temp		L temp
22	T	1,5			L temp	L temp		L temp
23				W	L ant temp	L ant temp		L temp

T = True; W = white matter lesion; R = right; L = left; MRI = medical temporal sclerosis; ant = anterior; no lat/loc = no lateralisation or localisation; temp = temporal.

1 High signal intensity in the hippocampus.

2 Smaller size of the hippocampus.

3 Hippocampal collateral white matter atrophy.

4 Enlarged temporal horn.

5 Diminished grey and white matter demarcation.

6 Smaller temporal lobe.

electrodes (DEEG) was performed. ^{18}F FDG PET and ^{11}C -flumazenil PET were performed in all of these patients. Nineteen patients were investigated with ^{123}I -iomazenil SPECT. Although all 23 patients were considered candidates for temporal lobe resective surgery, temporal surgery was carried out in 22; one patient was operated on in the temporal as well as the frontal lobe. The PET and SPECT studies have not been taken into consideration with respect to the presurgical diagnosis.

NEUROPHYSIOLOGICAL EXAMINATIONS

Scalp EEG

All patients were studied with long term interictal as well as ictal EEG-CCTV monitoring with conventional scalp electrodes, and anterior temporal and sphenoidal electrodes. The data were first assessed by one neurophysiologist. A final diagnosis was reached in a consensus meeting of the clinical neurophysiologists of the programme. Eighteen patients (6–23) had convergent findings in seizure semiology, ictal scalp EEG, and MRI that warranted surgery without DEEG.

Depth EEG

DEEG was carried out in five patients (1–5), according to the DEEG technique as described by van Veelen *et al.*² DEEG indicated a unilateral mesial temporal onset in one patient (5), a unilateral combined mesial and neocortical temporal onset in two patients (1,3), and a neocortical temporal onset in one other patient (2), whereas DEEG in the fifth patient (4) disclosed that epileptic seizures originated from the mesial and the neocortical temporal areas as well as the ipsilateral orbitofrontal region.

MRI

MR images were from a Philips Gyroscan 1.5 Tesla system with a regular headcoil. A protocol especially designed to visualise the temporal lobes was used.¹⁰ The MR images were reviewed by at least two radiologists blinded for the EEG lateralisation.

Abnormalities were detected in 22 of 23 patients (table 2). These were located in the temporal lobe in 20 and extratemporal lobe in three (6, 18, 23), including one patient (6) with combined temporal and extratemporal abnormality. One patient (1) showed no MRI abnormality.

In 18 patients the temporal lobe displayed the abnormalities characteristic of mesial temporal sclerosis. These abnormalities consisted of increased signal intensity of the hippocampus, atrophy of the hippocampus, and atrophy of the hippocampal white matter. In addition to these signs restricted to the mesial area of the temporal lobe, more widespread, medial temporal sclerosis related temporal abnormalities were detected—namely, an enlarged temporal horn, diminished grey and white matter demarcation, and a smaller temporal lobe.

In four patients (2, 5, 6, 7), only mesial temporal abnormalities were present. In these patients, three showed atrophy and increased signal intensity of the hippocampus. The fourth patient had only increased signal inten-

sity of the hippocampus. In 14 patients, in addition to mesial temporal abnormalities one of the signs of widespread temporal abnormality were seen. In two patients (4, 17), signs of widespread temporal abnormality other than medial temporal sclerosis were encountered. One patient (2) had a small calcified mesial temporal lesion, probably a small vascular malformation, which was detected in addition to medial temporal sclerosis.

Extratemporal abnormalities seen in three patients (6, 8, 23), were described as white matter abnormalities in all the patients concerned, probably without specific relevance. In one patient (6) abnormalities of white matter were combined with medial temporal sclerosis.

PRESURGICAL DIAGNOSIS

In 18 patients the presurgical diagnosis was reached on the base of non-invasive phase 1 studies (table 2). In patients with the epileptogenic area located “anterior temporally” the onset of the seizures was recorded on the sphenoidal electrode. In patients in whom the ictal onset was considered “temporal” a combined mesial and neocortical onset was recorded in the ictal scalp EEG. The results of the EEG and the MRI were combined to reach a phase 1 conclusion. In three patients (8, 11, 16) in whom ictal EEG localisation alone was insufficiently diagnostic, a combination of ictal EEG and MRI data warranted surgery without DEEG.

In patients 1–5 DEEG was performed because MRI and scalp EEG were not sufficiently concordant. After DEEG a final presurgical diagnosis was reached. In four patients DEEG showed a temporal onset. A fifth patient showed a combined temporal and ipsilateral orbitofrontal seizure onset. In patients with a temporal onset this was primarily mesiolimbic in one, combined mesiolimbic/neocortical in two, and only neocortical in one.

SURGERY AND POSTSURGICAL EVALUATION

Surgery included amygdalohippocampectomy and neocortical resection in all patients. Neocortical resection was guided by electrocorticography performed with a subdural subtemporal multicontact electrode forwarded to the hippocampal area in addition to the classic corticography. One patient (4) had a combined temporal and frontal resection. None of these patients, except patient 5, were considered candidates for a selective amygdalohippocampectomy only.

The seizure outcome after surgery was determined according to the criteria of Engel¹¹ in outcome class 1–4. Follow up ranged from 0.5–2.5 years (mean one year).

A pathological diagnosis of the resected mesial and neocortical temporal lobe was feasible in 21 of the 23 patients. In three patients the paucity of material did not allow a complete pathological diagnosis. Medial temporal sclerosis diagnosed in 15 patients was severe in most patients, according to the criteria proposed by Wyler.¹² Of these, only one patient (15) showed slight gliosis in the mesial tempo-

ral region. In two remaining patients; one (12) had a small mesial arteriovascular malformation (AVM), another (2) disclosed a mesial oligodendroglioma grade B (oligo B; table 3).

PET

Radiochemistry— ^{18}F -Fluorodeoxyglucose (^{18}FDG) was prepared by the nucleophilic reaction and the method of Hamacher *et al.*¹³ It yields no carrier added FDG without any contamination with ^{18}F -fluorodeoxymannose.

^{11}C -Flumazenil (^{11}C -Ro15-1788) was prepared by methylation of the *nor*-derivative (Ro 15-5528) by $^{11}\text{CH}_3$ I. About 130 mCi of the product were obtained within 40 minutes from the end of the bombardment. The radiochemical purity of the radiopharmaceutical was found to exceed 98% by thin layer and high pressure liquid chromatography. The specific activity at the time of injection was 895 (range 337–1721) mCi/ μmol . The equipment was designed to carry out the radiosynthesis automatically.

PET data acquisition—In the patients who used BZ medication this drug was withdrawn at least two weeks before the PET investigation. Before the start of the PET study, a thermolabile plastic face mask (Runtech, Liège) was moulded on the face of the patient. This mask ensures reproducible and stable positioning of the head in the desired position during the PET study. The patients were positioned into the gantry of a 951 CTI/Siemens tomograph. This scanner acquires 31 contiguous transaxial planes, 5 mm in thickness, with a 3.4 mm slice separation (centre to centre), simultaneously covering 11 cm of axial field of view.

The patient's head was placed in such a way that the most inferior plane of image acquisition passed through the orbitomeatal plane. The bed of the tomograph was then moved 1 cm more caudally in order to be certain to have all the tip of the temporal lobe in the field of view. Finally, the gantry of the tomograph was tilted -10° to -15° , so the transverse planes were acquired parallel to the long axis of the temporal lobe.¹⁴

Firstly, a 20 minute transmission scan was obtained for photon attenuation correction with three retractable rod sources containing 2.5 mCi ^{68}Ge each. Patients were then given a 10 ml solution with 20 mCi of ^{11}C -flumazenil intravenously in one minute. Dynamic scanning was started immediately with consecutive scans of increasing duration: 3×2 , 3×3 , 5×6 , and 2×11 minutes, total ^{11}C -flumazenil scanning time 75 minutes. At the end of this scan, 7.5 mCi ^{18}FDG were given intravenously. A static PET study was obtained from 30 to 60 minutes after injection. The total time needed for both PET studies was about 2.5 hours. The start of ^{11}C -flumazenil and ^{18}FDG scans was separated by 100 minutes or five half lives of ^{11}C -flumazenil. With the radioactive decay and without considering the biological washout, only 3.25% of the ^{11}C -flumazenil activity should be remaining when the ^{18}FDG scan started.

In this study no kinetic modelling was per-

formed, to reduce the burden for the patient as much as possible. A kinetic study would require at least two ^{11}C -flumazenil injections at two different specific activities. The radiation exposure would not allow an additional third injection. The protocol of this combined study was approved by the University Hospital ethics committee of the University of Liège.

Images were reconstructed with a Hanning filter with a cut off frequency set at 0.5. The smoothing effect of this filter is about 3 mm and this degrades the transverse resolution to 9 mm. A software algorithm allows for the reslicing of the study into coronal cuts.

PET was carried out in patients during the interictal state. Surface EEG could not be monitored during the PET acquisition period for technical reasons; however, all patients were continuously observed during the PET study by one of the investigators and none showed signs of clinical seizures. At the end of the study, each patient was asked whether any particular symptoms had occurred during the scanning period; none reported any sensation possibly corresponding with an aura or other seizure symptoms.

During both studies, blood samples were taken by the arterial catheter previously inserted in the radial or brachial artery under local anaesthesia. To characterise the plasma time-activity curves, a 2 ml arterial blood sample was obtained every 10 seconds during the first two minutes, every 15 seconds between two and three minutes, and then at 4, 5, 7.5, 10, 20, 30, 40, 50, and 60 minutes. The blood was centrifuged for about five minutes and 500 μl plasma counted with a Nal well counter.

PET data analysis

Cerebral metabolic rates for glucose were calculated pixel by pixel, using the operational equation of Phelps *et al.*¹⁵ as well as the rate and the lumped constants proposed by these authors for the adult man. Parametric images of glucose consumption were obtained.

The attenuation corrected ^{11}C -flumazenil images were decay corrected, transformed into maps of nCi/mCi using the appropriate calibration factor, and summed for the interval 17.5 to 55 minutes to enhance the anatomical details and to improve the statistical quality of the images. The summed ^{11}C -flumazenil and the ^{18}FDG parametric images were then reviewed independently by two authors of which one was blinded for the clinical data of the patient.

The analysis of the PET data was performed by visual and semiquantitative assessment of the metabolic images for the symmetry of glucose consumption and ^{11}C -flumazenil binding between homologous regions of the two hemispheres. A PET study was considered abnormal if an area of relative decrease in glucose metabolism or ^{11}C -flumazenil uptake could be seen on at least two contiguous PET slices. There was no disagreement between the investigators on which side the brain was affected.

The mesial temporal region was best identified on the ^{11}C -flumazenil scans. We therefore selected the transverse and the coronal planes passing through the hippocampus in the ^{11}C -

flumazenil scan and isolated the corresponding ^{18}F FDG slices. Regions of interest were then placed on the mesial and lateral cortex of the temporal lobe on the transverse slices, on the mesial, basal, and lateral part of the temporal lobe on the coronal slices. Asymmetry between homologous regions was calculated as $[(\text{right} - \text{left})/(\text{right} + \text{left})] \times 200$ and the asymmetry was rated as slight (5 to 14.9%), moderate (15 to 29.9%), or severe ($> 30\%$) (table 3). No region of interest was placed on the extratemporal areas.

SPECT

SPECT was performed during the interictal state with the central BZ antagonist ^{123}I -iomazenil, derived from flumazenil (Paul Scherrer Institute, Würenlingen, Switzerland). Retention within the brain at specific binding sites is about 7% of the administered dose at 80 minutes after intravenous injection. ^{123}I decays by electron capture and emits γ rays with an energy of 159 keV. In the patients who used BZ medication this drug was withdrawn at least two weeks before the SPECT investigation.

During the investigation ambient noise and light were reduced. A catheter was inserted into the antecubital vein allowing the injection of 4–5 mCi ^{123}I -iomazenil.

Data acquisition started 75–80 minutes after injection with a Picker PRISM 3000 three-detector rotating gamma camera, equipped with ultra high resolution fan-beam collimators, acquisition matrix 128×128 pixels, zoom factor 1, step and shoot acquisition; 3×20 steps, $6^\circ/\text{step}$, 20 s/view. The typical number of counts in a total study was about 3×10^6 .

SPECT data were reconstructed by a filtered back projection algorithm, using a Butterworth filter (5th order, 40% window). Attenuation correction was applied (0.12/cm). Transaxial slices were filtered (Ramp filter) and reoriented to "sagittal" (parallel to the midsagittal plane), "oblique transaxial" (parallel to the base of the brain), and "oblique coronal" (perpendicular to the two aforementioned directions) slice orientations. Slice thickness was 2 pixels, effective slice thickness 7.6 mm. Spatial resolution was 7 mm at FWHM.

The typical number of counts in the transaxial oblique slice at the level of the midtemporal gyrus was 100 k.

SPECT images were visually assessed by two independent examiners. In cases of disagreement a third interpreter was asked. The images were assessed for major focal or regional asymmetries. No such asymmetries were found in a control population consisting of nine subjects (age 22–33, mean 27 years).

Results

^{18}F FDG PET

^{18}F FDG PET was abnormal in all 23 patients. The hypometabolism, expressed in degree of abnormality 1, 2, or 3, was always unilateral and in agreement with the lateralisation and lobe of surgery (table 3). With these degrees of abnormality the area with maximum hypometabolism could be indicated.

Hypometabolism was restricted to the temporal areas in 13 patients. In addition to temporal hypometabolism extratemporal hypometabolism was detected in 10; although in eight of these the maximum abnormality was intratemporal. In two patients (4,21) the abnormality was equally pronounced in temporal and frontal areas; one with a frontal and temporal focus, another with a single focus in the temporal lobe.

In 21 patients with maximum hypometabolism in the temporal lobe, this maximum was mesial in one and neocortical temporal in nine, whereas in most (11 patients) the hypometabolism was equal in mesial and neocortical areas. In none of the 23 patients an anterior temporal ictal onset in scalp EEG, characterised by initial ictal changes on the ipsilateral sphenoidal electrode, was related to a maximum hypometabolism in the mesial temporal area.

^{11}C -FLUMAZENIL PET

All ^{11}C -flumazenil PET scans showed unilateral decreased BZ receptor binding. It was restricted to the temporal lobe in 21 of 23 patients. Extratemporal abnormality was detected in two patients (15,17) but the abnormality was always maximal in the temporal lobe. The temporal lobe indicated by ^{11}C -flumazenil PET as abnormal was identical with the lobe of surgery in all cases.

Transverse scans disclosed a predominantly or exclusively decreased BZ receptor binding in the mesial temporal area in all patients except one, who was the only one who had a tumour (an oligodendroglioma in the mesial temporal lobe).

Coronal ^{11}C -flumazenil PET scans, which provided a more detailed view of subdivisions of the temporal lobe, were abnormal in 21 patients, whereas two were normal. Abnormality seen in the 21 patients was maximal in the mesial temporal region in 18. Of these 18, 13 demonstrated abnormality restricted to the mesial temporal region. In general the extension of decreased receptor binding was less in coronal scans compared with transverse sections. There proved to be no consistent relation between mesiocortical or neocortical temporal PET findings and anterior temporal EEG onset. Nine patients with an anterior temporal onset in scalp EEG, characterised by initial ictal changes on the ipsilateral sphenoidal electrode, demonstrated a maximum of abnormality in the mesial temporal area. This mesial temporal abnormality was not specific for this group of patients and was often seen in patients with a more widespread ictal onset in the temporal lobe.

^{123}I -IOMAZENIL SPECT

SPECT was performed in 19 patients (table 3). A minority of patients had a SPECT abnormality of which the localisation was related to the side of the lesion as established by the methods indicated above. This correlation was correct in only six of 19 patients. In another three of these 19 patients SPECT indicated the epileptogenic lobe as abnormal;

Table 3 Functional imaging, seizure outcome, and pathology

Patient no	FDG PET (transv)			FDG PET (cor)			Flum PET (transv)			Flum PET (cor)			PET lat	SPECT Temp abn in resected lobe	SPECT False lat/loc no abn	SPECT Extra temp abn	Postsurgical data	
	Mesial Temp	Lateral Temp	Extra Temp	Mesial Temp	Basal Temp	Lateral Temp	Mesial Temp	Lateral Temp	Extra Temp	Mesial Temp	Basal Temp	Lateral Temp					Out-come Engel class	Path-ology Wyler class
1	1	1		1			2			2			R	T			1	No diagn
2		1			3	1	2			1	3		R		Lat		1	oligo B*
3	2	2	1	2	2	2	2	1		2			R	T			3	MTS (4)
4		1	1		1	1	1			1			R		No abn		4	No diagn
5	2	1		2	1		2	2		2	1	1	L	T			1	MTS (3)
6	1	1			1			1		1			R		Lat		1	MTS (3)
7	2	2		1	1		2						R		Bilat		1	MTS (3)
8	3	3		3	3	3	3	1		2	2	1	R	T			1	MTS (3)
9	1	3	1	1	2		2			1			R	T			1	MTS (4)
10		1		1			1						R	T			1	MTS (3)
11	1	1		1	1		2	1		1			R		Bilat		1	MTS (4)
12		2	1	1	2	2	1			2	1		R		Lat	Lat	1	AVM
13	1	1		2	2	2	2	1		2	1		R		Lat		1	MTS (4)
14	1	2		2	2	1	2	1		2			R		Lat		1	MTS (4)
15	2	2	1	1	2	2	2		1	1			R				1	MTS (1)
16	2	2	1	2	2	2	2			2			R				1	MTS (3)
17	2	2	1	2	2	2	2	1	1	1	2	2	R	T		Lat +	1	MTS (3)
18	1	2		1	1	1	1			1			R		Lat	Lat -	3	No abn
19	1	2		2	2	2	2	1		2	1		L				1	MTS (4)
20		1		1			2			1			L		Bilat		1	MTS (4)
21		1	1	2	2	2	2	1		2			L	T		Lat -	1	MTS (4)
22	2	2	1	2	2	2	2	1		2	1		L				1	MTS (4)
23	2	3	1	2	3	1	2	1		1			L	T		Lat +	1	No abn

Degree of abnormality in PET: 1 = slight (5–14.9%); 2 = moderate (15–29.9%); 3 = severe (> 30%). Seizure outcome class: 1 = seizure free; 2 = sporadic seizures; 3 = > 90% improved; 4 = not improved. Pathology MTS class: 1 = slight; 2 = mild; 3 = moderate; 4 = severe. transv = transverse plane; cor = coronal plane; R = right; L = left; T = true; temp = temporal; lat+ = correct lateralisation; lat- = incorrect lateralisation; MRI diagnosis MTS not confirmed due to insufficient material; abn = abnormality.

however these three had an equal expression of ipsilateral extratemporal abnormality (correct lateralisation: lat+, table 3) as well. In nine patients the lateralisation was incorrect and in one patient SPECT indicated no abnormality.

COMPARISON OF ¹⁸FDG PET, ¹¹C-FLUMAZENIL PET, ¹²³I-IOMAZENIL SPECT, AND OUTCOME AFTER SURGERY

By contrast with the accuracy demonstrated by ¹⁸FDG PET and ¹¹C-flumazenil PET in localising the side and lobe where the epileptogenic zone was found, ¹²³I-iomazenil SPECT was inaccurate in this respect as described in the previous section.

These conclusions are supported by the outcome data: 87% were seizure free. This seizure outcome indicated that surgery was correctly performed in the epileptogenic region in these patients. In three of the 23 patients (13%) with minor or no improvement, analysis allowed no definite conclusions

why surgery was ineffective, except for patient 4, in whom the postsurgical MRI disclosed an incomplete resection of the amygdalo-hippocampus complex. The relation between outcome and the extent of amygdalohippocampectomy could not be analysed in detail as no volumetric MRI studies after surgery were performed.

COMPARISON OF IMAGING TECHNIQUES AND DEEG

DEEG was performed in five patients. In these patients the relation between area of seizure onset and results of PET techniques was analysed in detail (table 4). The area of seizure onset was described as mesial temporal, neocortical temporal, or extratemporal.

Hypometabolism in ¹⁸FDG PET proved to be more extensive than the epileptogenic region indicated by DEEG in two patients, was equally extensive in two, and was more restricted in one. In ¹¹C-flumazenil PET the abnormal region was more extensive in two, equal in one, and less extensive in two patients.

Extratemporal hypometabolism detected with ¹⁸FDG PET was not detected by ¹¹C-flumazenil PET in these five patients.

Although the number of patients examined with DEEG was limited, no clear differences between the results obtained with this method compared with those of ¹¹C-flumazenil PET and ¹⁸FDG PET were encountered.

¹⁸FDG PET, ¹¹C-FLUMAZENIL PET, AND PATHOLOGY

A pathological diagnosis was obtained in 21 patients; in 17 mesial temporal sclerosis, in one an oligodendroglioma grade B, in another a vascular malformation, and in two patients no abnormalities were found (table 3).

In six patients with mesial temporal sclerosis, ¹⁸FDG PET demonstrated additional extra-

Table 4 Comparison of DEEG and PET localisation

Patient No	Mesial T	Neocort T	Extra T
1			
DEEG			
FDG PET			
Flum PET			
2			
DEEG			
FDG PET			
Flum PET			
3			
DEEG			
FDG PET			
Flum PET			
4			
DEEG			
FDG PET			
Flum PET			
5			
DEEG			
FDG PET			
Flum PET			

T = Temporal; ■■■■ = abnormal area.

Figure 1 ^{18}F FDG PET, ^{11}C -flumazenil PET, and ^{123}I -iomazenil SPECT studies in patient 23, demonstrating the abnormality in the coronal plane of the left temporal lobe; the abnormality in ^{11}C -flumazenil PET was restricted to the mesial temporal (hippocampal) area.

temporal hypometabolism. The maximum hypometabolism was in the temporal lobe in five, but in one patient it was equally present in the frontal and temporal lobes.

In two patients with mesial temporal sclerosis, areas with decreased benzodiazepine receptor binding were located in the mesial and neocortical part of the temporal lobe and extended to extratemporal areas as well. In two patients without abnormality in the pathological examination ^{11}C -flumazenil PET showed areas with reduced benzodiazepine binding maximally in the mesiotemporal area.

Although all 21 patients with pathological abnormality showed hypometabolic zones with ^{18}F FDG PET and a decreased uptake in ^{11}C -flumazenil binding, there was no direct relation between pathological diagnosis and

functional abnormality in PET. Presence and classification of mesial temporal sclerosis in the pathological specimen could not be predicted from the results of functional imaging. In two patients without pathological abnormality PET techniques indicated areas of abnormal function.

Discussion

GENERAL ASPECTS: CONCLUSIONS OF MRI AND EEG AND OF PET AND SPECT IN RELATION TO THE ASSESSMENT OF AN EPILEPTOGENIC REGION

A prerequisite for resective surgery in partial epilepsy is the precise identification of the zone of ictal onset. Recording DEEG is considered to be the most reliable method of

Figure 2
Electrocorticogram in patient 1: eight neocortical electrodes (common reference skull) presenting no epileptic abnormality, one depth electrode in the hippocampal area showing abundant spiking.

achieving this goal. However, due to the invasive character of this method, various less invasive evaluation techniques have been pursued to provide a suitable alternative. These methods are included in the non-invasive phase of the presurgical evaluation. Abnormalities on MRI, especially signs of medial temporal sclerosis, combined with concomitant ictal seizure onset in EEG monitoring, is considered an excellent predictor of good outcome after surgery.¹⁶ Combination of these MRI and EEG variables warranted surgery without DEEG in a group of 18 out of 23 patients in the present study. In five patients, DEEG was performed because the ictal scalp EEG was not sufficiently localising, despite the presence of a localised temporal abnormality in the MRI.

The present study enables us to give an answer to the question of whether and to what extent imaging methods ¹⁸FDG PET, ¹¹C-flumazenil PET, and ¹²³I-iomazenil SPECT can contribute to the presurgical evaluation in patients with medically intractable complex partial seizures. The starting point for this comparative analysis is the assessment of phase 1 based on MRI and on ictal EEG recordings (table 2). In all cases the ¹⁸FDG PET yielded the concordant result in respect to the side of the abnormality (table 3). The same applies to the ¹¹C-flumazenil PET but not to the ¹²³I-iomazenil SPECT. Concerning the lobe of onset: ¹⁸FDG PET localised incorrectly in one patient (21) and in ¹¹C-flumazenil PET in none. In SPECT the lobe of onset correlated with the other methods in only nine of the 23 patients; in the others the lateralisation was the opposite in six, inconclusive due to a bilateral abnormality in three, and in one no abnormality was detected. Therefore we conclude that the present SPECT technology using ¹²³I-iomazenil as ligand does not contribute to the presurgical evaluation in this group of patients.

A detailed comparison between the conclusions of phase 1 (MRI and EEG) and the results obtained using the two PET methods is not simple as it cannot be specified whether the lesion was mainly mesial, neocortical (basal or lateral), or temporal. Considering all cases jointly ¹⁸FDG PET tends to detect a more extensive area of abnormality than ¹¹C-flumazenil PET; this occurred in 17 of the 23 patients, whereas in five both detected roughly equal areas and in one (5) only ¹¹C-flumazenil PET indicated a more extensive abnormality. In none of the patients with an anterior temporal ictal onset in scalp EEG did ¹⁸FDG PET show a maximal hypometabolism in the mesial temporal area. The mesial abnormality with ¹¹C-flumazenil PET correlated in these patients with an anterior temporal onset in scalp EEG but was not specific, because this was also seen in patients with a more widespread ictal onset in the temporal lobe.

PERFORMANCE OF IMAGING METHODS IN COMPARISON WITH DEEG

A more detailed analysis is possible in those patients in whom DEEG analysis was carried out (table 4). A perfect coincidence existed between areas detected as abnormal by the ¹⁸FDG PET and those obtained by DEEG methods. In only two patients (1,2). In two patients (3,5) the areas detected by ¹⁸FDG PET were more extensive than those indicated as abnormal by DEEG and in one too limited. The ¹¹C-flumazenil PET areas detected as abnormal were the same as with DEEG in one, more extensive in two, and less extensive in two patients. In the five patients in whom DEEG was performed the ¹¹C-flumazenil PET was not more restricted than with ¹⁸FDG PET. The results of these DEEG studies also indicate that an evaluation of functional imaging methods based on scalp EEG results alone is unreliable. Scalp EEG could not indicate the lobe of onset in three of these five patients.

In the two other patients the localisation with scalp EEG was insufficient and indicated a possible multifocal or posterior temporal onset. For all patients presented, five of 23 (22%) needed DEEG recordings to bypass filtering by structures covering the brain and to enable recording in the vicinity of the focus.

COMPARISON BETWEEN PET AND SPECT

With ^{18}F FDG PET, areas of decreased CMRglu, consistent with the lateralisation or even the localisation of the primary epileptic focus have been demonstrated.^{17–20} However, the hypometabolism is often widespread, which limits the localising capacity of this technique.

Flumazenil is a benzodiazepine receptor antagonist, blocking the effect of both agonists and inverse agonists at benzodiazepine receptors while having little pharmacological effect on its own. Labelled with ^{11}C it is an excellent radiolabel to image benzodiazepine receptors in vivo with PET.²¹ A comparison between PET and SPECT techniques using related ligands is necessary to establish the effectiveness of these techniques in presurgical evaluation. PET has several drawbacks compared with SPECT, such as higher costs and restricted accessibility due to limited facilities. The SPECT technique, more widely available, might enhance selection of candidates for epilepsy surgery, if ^{123}I -iomazenil SPECT was equally effective as ^{18}F FDG PET or ^{11}C -flumazenil PET. Comparative studies of ^{18}F FDG PET and ^{11}C -flumazenil PET in patients with complex partial seizures have been limited so far.^{6,7,9} In a comparison between ^{18}F FDG PET, ^{123}I -iomazenil SPECT, and DEEG, van Huffelen *et al*⁵ found that, in a study limited to eight patients, SPECT showed a correct lateralisation in 87.5% (seven of eight), whereas PET always demonstrated ipsilateral hypofunction. Due to its limited spatial resolution or the extent of the abnormality concerned, ^{123}I -iomazenil SPECT was considered primarily useful in identifying the side of epileptic focus.

PET as well as SPECT techniques have been improved recently by the introduction of second generation technology. Besides the use of ^{18}F FDG PET, direct comparison of two methods, ^{11}C -flumazenil PET and ^{123}I -iomazenil SPECT, which are based on the hypothesis that changes in identical BZ receptor sites are displayed, became feasible.

In this study of 23 patients hypometabolism of ^{18}F FDG PET was found to be more extensive, with abnormality outside the lobe of surgery in nine patients. This is by contrast with the abnormal region indicated by ^{11}C -flumazenil PET, which was topographically more restricted. Extension of abnormality outside the lobe of surgery was seen in only two of the 23 patients with this technique and turned out to be less severe compared with the temporal abnormality. DEEG studies indicate that a localised onset in the mesial or neocortical temporal region of seizures cannot be predicted in a reliable way by functional imaging with ^{18}F FDG or ^{11}C -flumazenil PET.

It is worthwhile noting that in the only patient (4) with a temporal as well as a frontal focus the correlation with ^{18}F FDG PET was accurate whereas ^{11}C -flumazenil PET only correlated with the temporal and not with the frontal epileptogenic area. This may indicate that the results of ^{11}C -flumazenil PET might be less valuable in patients with an extratemporal origin of their seizures. The sensitivity of this method in extratemporal epilepsy remains to be evaluated.

The results obtained in the present study show partial agreement with previous studies,^{7,8} which stated that the area of decreased uptake in ^{11}C -flumazenil binding is more restricted and has a closer spatial relation with the zone of ictal onset than the area of glucose hypometabolism. In five patients of our study in which DEEG was performed the ^{11}C -flumazenil PET was not more restrictive as regards the detection of abnormality in DEEG in comparison with ^{18}F FDG PET.

^{123}I -Iomazenil SPECT was highly inaccurate in localising the lobe of surgery. Despite introduction of second generation technology the insufficient localising capacity of interictal ^{123}I -iomazenil SPECT clearly restricts the applicability in presurgical evaluation of epileptic patients.

The difference in localising capacity in this limited group of patients between ^{11}C -flumazenil PET and ^{123}I -iomazenil SPECT is striking, because both methods apply BZ receptor ligands. Actually, there is no definite explanation for this phenomenon, although several interpretations are conceivable. Possible factors for discrepant results are: (a) differences in molecular structure of ligands caused by adherence of different elements, a small F molecule compared with a larger I molecule, that results in divergent BZ receptor binding; (b) differences in activity level or acquisition. Activity dose administered in ^{123}I -iomazenil SPECT is lower compared with activity dose in the ^{11}C -flumazenil PET technique. Onset of scanning after injection of the ligand is later in ^{123}I -iomazenil SPECT compared with ^{11}C -flumazenil PET. Furthermore, the PET technique is characterised by a more efficient data acquisition system, resulting in a better signal to noise ratio than SPECT, which necessitates the use of collimators. Attenuation correction is considered a major problem in SPECT compared with PET. A question is whether future research with an improved interictal ^{123}I -iomazenil SPECT technique or the application of ictal ^{123}I -iomazenil SPECT, will show results more similar to ^{11}C -flumazenil PET. The reduced level of costs and the relatively easy access to SPECT facilities will activate this research.

Our results suggest that the decrease in ^{11}C -flumazenil binding seems related to the neuronal loss accompanying the epileptic focus rather than to the epileptogenicity of the involved area. These results are in line with autoradiographic studies showing a decrease of 3H-Ro 15–1788 that correlated with neuronal loss in resected tissue of patients with temporal lobe epilepsy.^{22,23}

Conclusions

This study illustrates that single methods as part of non-invasive presurgical evaluation may have limited localising capacity. Convergence of the results of different methods can improve the ability to indicate the localisation of the focus with more precision. In the Dutch programme only the convergence of EEG and MRI techniques was used in clinical practice. Although Engel²⁴ has indicated that ¹⁸FDG PET is an important and reliable confirmatory test in the presurgical evaluation, this technique is not yet included in the present protocol as a factor in the routine process of clinical decision making in order to enable the comparison of different PET and SPECT techniques. ¹⁸FDG PET and ¹¹C-flumazenil PET turned out to be reliable for localisation of epileptogenic temporal lobe, which supports the presurgical diagnosis in patients with non-lesional MRI or non-lateralising/localising scalp EEG recordings. In those patients whose phase I presurgical evaluation allows no localisation of the epileptogenic area, PET studies may provide topographical information for the planning of the implantation of intracranial electrodes for DEEG. Further application of both PET techniques in combination with DEEG is required to elucidate the discrepancy between transverse and coronal scans and to evaluate the abnormalities in patients with extratemporal epileptic seizures.

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