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Combined study of ^{99m}Tc-HMPAO SPECT and computerized electroencephalographic topography (CET) in patients with medically refractory complex partial epilepsy

Margarida RODRIGUES,* M. Moniz BOTELHO,** Ana T. FONSECA,* John P. PETER,**
Teresa PIMENTEL** and M. Rosário VIEIRA*

*Department of Nuclear Medicine and **Department of Neurophysiology,
Portuguese Institute of Oncology, Lisbon, Portugal

For successful surgery for drug-resistant partial epilepsy the site of the seizure focus needs to be known exactly. The purpose of this study was to compare the evaluation of the regional cerebral blood flow (rCBF) (localization and degree of disturbances) by ^{99m}Tc-hexamethylpropyleneamineoxime (HMPAO) single photon emission computed tomography (SPECT) with computerized electroencephalographic topography (CET) and transmission computed X-ray tomography (CT) in partial epilepsy.

The study included 20 patients with medically refractory complex partial seizures. Of the 20 patients included, 15 were studied interictally, four ictally and one in both states, interictally and ictally.

^{99m}Tc-HMPAO SPECT detected rCBF changes in 95% of the patients. Interictal studies demonstrated focal areas of hypoperfusion in 93% of the patients. Ictal studies demonstrated an area of hyperperfusion in all patients. Blood flow disturbances in deeper structures of the brain, such as basal ganglia, could be detected. The areas with abnormal ^{99m}Tc-HMPAO uptake were concordant, in localization, with CET in 85% of the patients. Abnormal data with CT scans were found in only 45% of the patients. Focal lesions were found in 20% of the patients by CT scans.

^{99m}Tc-HMPAO SPECT combined with CET may be a useful screening procedure prior to referral for invasive diagnostic procedures in future management of patients with medically refractory complex partial seizures.

Key words: brain imaging, SPECT, HMPAO, computerized EEG, partial epilepsy

INTRODUCTION

FOCAL EPILEPSY is a condition where patients suffer from partial seizures, originating in a focus in the brain, usually in the temporal lobe. The focus generates uncontrolled electric activity spreading over other brain areas.[1] From 30% to 60% of patients with complex partial seizures ultimately become refractory to medical treatment and may be referred for surgical removal of a discrete seizure focus. Successful excision of well-localized foci leads to the elimination of seizures or significantly improved pharmacological control in 80% of surgical patients.[2,3]

Current noninvasive techniques for localizing seizure foci, including electroencephalogram (EEG), transmission computed X-ray tomography (CT) and magnetic resonance imaging (MRI) are often inadequate. In order to more accurately identify the seizure focus, many patients undergo implantation of subdural or intracerebral depth electrodes with prolonged video and EEG monitoring.[4] This method is invasive, with possible complications such as intracerebral bleeding and infection,[1] is costly, and subject to significant sampling error.[4,5]

Interictal single photon emission computed tomography (SPECT) regional cerebral blood flow (rCBF) imaging seems to be the most convenient and cost-effective technique for the localization of a temporal lobe focus in adult patients with medically refractory complex partial

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For reprint contact: Dr. Margarida Rodrigues, Bruenner Strasse 140–62–22, A-1210 Vienna, AUSTRIA.

seizures. Studies to date would suggest that, when an area of focal temporal lobe hypoperfusion is observed, the need for further studies is minimal (particularly if the scalp EEG is concordant).[3]

Computerized electroencephalographic topography (CET) is a method that defines a brain map based on areas of electric activity. Brain mapping of paroxysmal discharges can lead to improved precision concerning the spacial onset of a discharge and a clear idea of the associated field, providing a better understanding of the possible localization of the neuronal generators.[6]

^{99m}Tc-hexamethylpropyleneamineoxime (HMPAO) SPECT and CET comparative studies may provide valuable information concerning the pathophysiology and future management of epilepsy. The purpose of this study was to compare in patients with medically refractory complex partial epilepsy the localization and degree of rCBF disturbances detected by ^{99m}Tc-HMPAO SPECT with CET and CT scans, representing functional and morphological imaging methods, respectively.

PATIENTS AND METHODS

The study included 20 patients (12 females and 8 males) with an age range from 11 to 63 years old (average of 35.7 years) with medically refractory complex partial seizures. The disease duration was 2–14 years and the age of onset was 8–52 years. No patient had associated syndromes.

Every patient underwent ^{99m}Tc-HMPAO brain SPECT, CET and CT scans studies.

In 15 patients ^{99m}Tc-HMPAO SPECT and CET were performed interictally. Four patients were studied ictally (presenting clinical manifestations). One patient was studied in both stages, ictally and interictally. The patients studied in the interictal period were seizure free for 5–30 days. In the ictal period, the tracer was administered 2–10 minutes within the seizure.

The time interval between SPECT and CET was 30 minutes to 24 hours. The CT scans were obtained within 5 days (mean 2.6 days) from the corresponding ^{99m}Tc-HMPAO SPECT studies.

Technetium 99m HMPAO (Ceretec^{R}; Amersham UK) was prepared according to the manufacturer's recommendations. The HMPAO freeze dried kit was reconstituted with pertechnetate ^{99m}Tc solution, and a dose of 15–25 mCi (555–925 MBq) was injected within 30 minutes of tracer preparation in an antecubital vein. For application patients were placed in the supine position in a quiet room with dimmed light.

SPECT was carried out between 15 and 45 minutes after the injection. Patients were positioned manually with the orbitomeatal line perpendicular to the plane of the camera face. The radius of rotation used was reduced to an absolute minimum for each patient. For data acquisition a single head camera (General Electric (GE) STARPORT or GE 400T) was used (360° rotation, 64 single projection images, 64 × 64 matrix, low-energy high-resolution collimator, 140 ± 20% KeV window). Time per projection was 30 seconds. With standard GE software, horizontal (transversal), coronal and sagittal slices, each 6.25 mm, were reconstructed by filtered back-projection employing a Butterworth filter with a cut-off-frequency of 0.2 cycles/pixel. Attenuation correction was performed. The monitor display format had a 16 component color scale with white representing the maximum of reconstructed activity. The color display level was individually adjusted for each patient so that the central area of the cerebellum was white, thus normalizing the entire data set to the 99mTc-HMPAO activity in the cerebellum. The SPECT images were evaluated qualitatively and semiquantitatively. Visual image interpretation included transaxial, coronal and sagittal views describing locations of reduced or increased uptake relative to the cerebellum and/or contralateral brain. An increased tracer accumulation was interpreted as increased blood flow, and decreased accumulation as decreased blood flow, respectively. In addition, for semiquantitative evaluation, regional tracer uptake was measured, according to the method of Bottger et al.,[7] with minor modifications. Semiquantitative analysis of the data revealed either normal, slightly bilateral inhomogenous regional perfusion, slight regional hypoperfusion or hyperperfusion (side difference 2–4/16 steps/scale, equal to 12.5–25%), moderate regional hypoperfusion or hyperperfusion (side difference > 4–8/16 steps/scale, equal to > 25–50%) or marked regional hypoperfusion or hyperperfusion (side difference > 8–16/16 steps/scale, equal to > 50–100%).

CET studies were performed in Biologic Brain Atlas III, with a software that includes two menus of EEG and fast Fourier transformer. The acquisition of the information was recorded from 19 leads according to the International 10/20 system referenced to linked chins electrodes. Patients were alert but resting quietly in a dimly lit room.

CT scans were obtained by using standard techniques and were performed by the same neuroradiologists.

Informed written consent for the studies was obtained from each patient.

RESULTS

Comparison between ^{99m}Tc-HMPAO SPECT data and CET and CT scan findings are shown in Table 1.

rCBF focal abnormalities were observed by ^{99m}Tc-HMPAO SPECT in 19/20 patients. In 8 patients the pathologic region was found in the right side, in 6 patients in the left side and in 6 patients in both sides. Basal ganglia hypoperfusion was observed in 4 patients.

Interictal ^{99m}Tc-HMPAO SPECT demonstrated focal areas of hypoperfusion in 14 patients (Fig. 1) and a focal area of hyperperfusion in one patient (Patient no. 15, Table 1). CT showed a tumoral lesion in this patient. Another patient (Patient no. 16, Table l) had a slightly

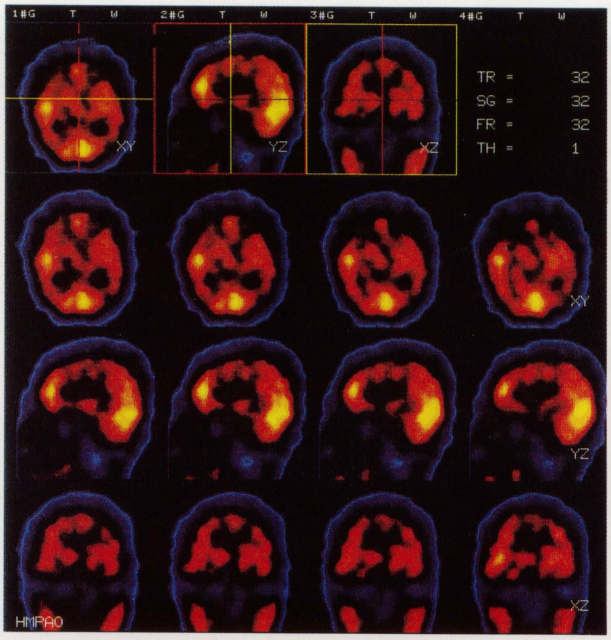

Fig. 1 Interictally ^{99m}Tc-HMPAO SPECT scanning showing slight hypoperfusion of the left temporal lobe (Patient no. 8a).

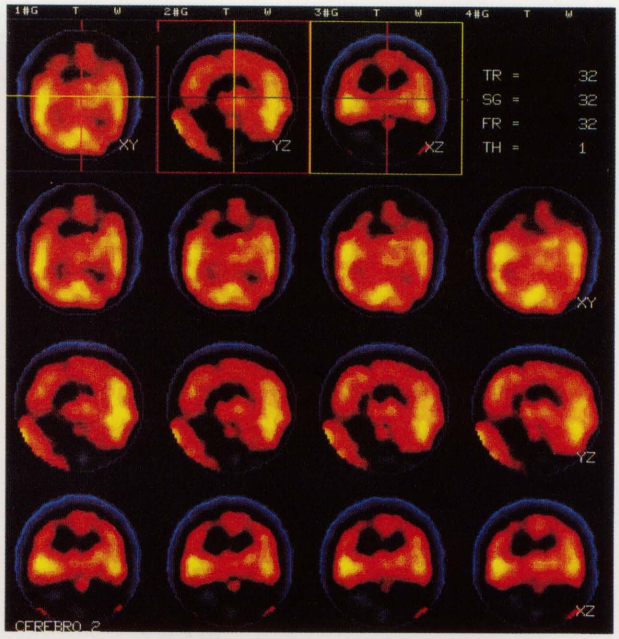

Fig. 2 ^{99m}Tc-HMPAO SPECT carried out during an ictal phase showing increase in signal in the anterior, mesial and lateral aspects of the left temporal lobe (Patient no. 8).

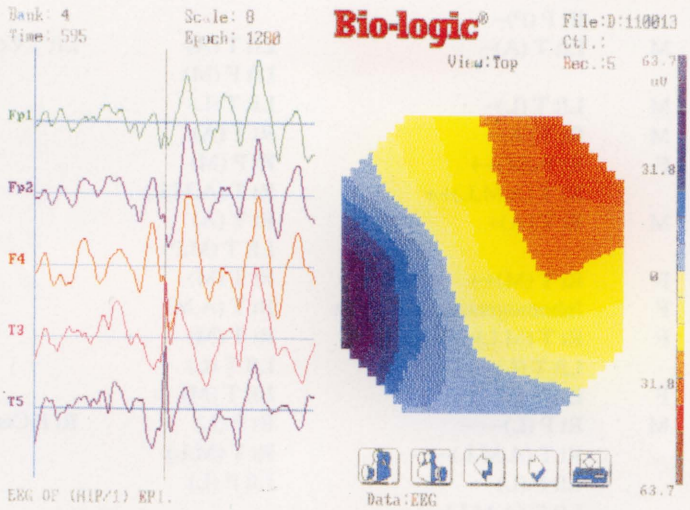

Fig. 3 CET study demonstrating a focus with the activity in the left temporal lobe. The focus generates a dipole oriented from left temporal towards right frontal region; this localizes the dipole source very deep in the left temporal area (Patient no. 8a).

bilateral inhomogenous perfusion without any focal abnormality.

The ictal ^{99m}Tc-HMPAO investigation demonstrated an area of hyperperfusion in all patients (n = 5) (Fig. 2).

CET demonstrated abnormalities in all the 20 patients studied (left side 10 patients, right side 7 patients, bilateral 3 patients) (Fig. 3).

There was complete agreement between the ^{99m}Tc-HMPAO SPECT and the CET studies in 8 patients. In 2 patients (Patients nos. 4 and 6, Table 1) the former localized the epileptic focus in the right side, opposite to the CET finding. No focal lesion was found by CT in these 2 patients.

The extension of the abnormal perfusion detected by ^{99m}Tc-HMPAO SPECT in 8 patients was larger than the corresponding abnormality detected by CET.

CT scan was normal in 11 patients. Focal lesions (low density areas (n = 4) and high density spot (n = l)) were found in 4 patients by CT (Fig. 4).

Table 1 ^{99m}Tc-HMPAO SPECT findings compared to CET and CT scan in 20 patients with partial epilepsy

Patient no.	Age	Sex	SPECT	CET	CT
1	47	M	Lft F (A,M,L)––– Lft P (A,M)–– Lft T (M)––	Lft F (A,M,L) Lft P (A) Lft T (M)	Lft F Cortical/subcortical atrophy
2	32	F	Rt T (M,L)–– Rt B–	Rt T (M)	N
3	53	M	Lft P (P)– Lft T (A,M)– Lft B–	 Lft T (M)	N
4	33	F	Rt T (M)– Rt B–	Lft T (M)	N
5	34	F	Lft T (A)– Rt T (A)– Rt B–	Lft T (A,M)	N
6	13	M	Rt P (M)–	Lft T (A)	Rt P, Lft T Cortical atrophy
7	14	F	Rt P (M)–– Rt T (M)–– Lft O–	Rt P (M) Rt T (M)	N
8	46	F	Lft T (A,M,L)++ Rt P (P)– Rt T (M,L)–	Lft T (A,M,L)	Lft T Focal lesion
8a	46	F	Lft T (M,L)–	Lft T (M,L)	Lft T Focal lesion
9	45	F	Lft T (M)+ Lft P+ Lft O–– Rt P (P)–	Lft T (M,P)	N
10	28	M	Lft T (A)–	Lft T (A) Lft F (M)	Lft T Cortical/subcortical atrophy
11	11	M	Lft T (L)–	Lft T (L)	N
12	17	M	Rt T (A)–	Rt T (A)	N
13	24	F	Rt P (M)++ Rt T (A,M,L)++	Rt P (M) Rt T (A,M,L)	N
14	42	M	Rt T (A)+	Rt T (A) Lft T (M,P)	N
15	29	F	Rt T (M)++	Rt T (M)	Rt T Focal lesion
16	15	F	Inhomogeneous perfusion	Rt T (A,M)	Rt T Focal lesion
17	63	F	Rt T (M,L)–– Lft T (L)––	Rt T (M) Lft T (L)	Rt T Focal lesion
18	53	F	Lft T (M)+	Lft T (M)	N
19	61	M	Rt P (L)––– Rt T (A,M,L)––– Lft P (L)–– Lft T (A,M,L)––	Rt P (L) Rt T (M,L) Lft P (L)	Rt P Cortical/subcortical atrophy
20	53	F	Rt T (M,L)–	Rt T (M,L)	Rt T Cortical atrophy

Lft, left side; Rt, right side; F, frontal lobe; T, temporal lobe; P, parietal lobe; O, occipital lobe; B, basal ganglia; A, anterior; M, mesial; L, lateral; P, posterior; N, normal; –––, marked hypoperfusion; ––, moderate hypoperfusion; –, slight hypoperfusion; +, slight hyperperfusion; ++, moderate hyperperfusion; +++, marked hyperperfusion; a, the same patient.

DISCUSSION

As surgery becomes more widely utilized as a treatment for drug-resistant partial epilepsy,[5] the challenge remains to improve methods for accurate localization and prediction of outcome. Each year, approximately 500/500,000 patients with medically refractory complex partial seizures receive surgery in the United States, partially due to the difficulty of adequate focus localization.[3]

Data on the frequency of positive findings with CT and MRI in partial epilepsy vary widely in the literature. For CT most authors report positive findings in about 30%–40% of the patients. The frequency of positive MRI findings is reported by most authors to be about 70%–80%.[8] In our study, we found abnormal data with CT in 45% of the patients. Focal lesions were found in 20% of

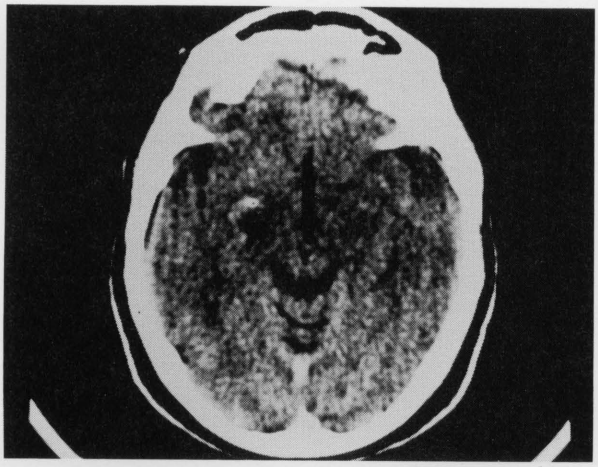

Fig. 4 CT scan showing a low density area and a small high density spot in the left temporal lobe (Patient no. 8).

the patients.

The increased regional electrical activity requires localized increased cerebral metabolism, which in turn requires increased blood flow.[9] Conventional EEG recording methods are very specific for partial epilepsy but good quality EEG cannot always be achieved and correct lateralization of a focus is in some situations difficult.[2,8] Scalp EEG may be misleading in the localization of the primary site of seizure onset because it has inherently low spatial resolution and is fundamentally dependent upon primarily cortical surface effects.[3] Surface electrocorticography is also limited by the area of the brain sampled and its sensitivity to and localization of deep-lying generators.[3,9] Even intracerebral EEG, an extremely invasive method, is inaccurate as a localizing method in 10%–20% of all cases.[8] It can monitor deeper structures but samples only limited regions of the brain.[3] In CET, for topographic brain mapping, the EEG electrical potentials are obtained from 19 scalp electrodes. These data are then processed by a computer, which graphically displays them on a color video screen. We used linear interpolation to determine the electrical potential values between electrodes. This renders the electrical activity on the surface of the scalp far easier to comprehend. Power spectral maps obtained with CET provide detailed information about the frequency content of the EEG signal enhancing slight differences between the frequency structure of the two hemispheres. The topographic map display summarizes information and enables a better correlation between functional and anatomical diagnostic data.[6,10] Other methods, which use the electric activity of the brain, for example magnetoencephalography, are still in the experimental stage.

Nuclear medical methods, such as the mapping of regional brain metabolism by positron emission tomography (PET) or the brain imaging of rCBF by ^{99m}Tc-HMPAO SPECT, are increasingly being used as adjunctive techniques in the localization of seizure foci. PET and SPECT noninvasively provide physiologic and anatomic information about the seizure focus. Although ictal PET scans may identify seizure foci successfully,[4] these studies are not generally available due to the high cost, the need of a cyclotron, and the short half-life of positron emitters.

HMPAO is a lipophilic compound that crosses the blood-brain barrier, becomes readily absorbed into cell membranes and is retained in tissue. Regional uptake of ^{99m}Tc-HMPAO is proportional to the flow of blood to a given area.[11] It is not specific for epileptic changes of the brain. The patients selected for the study had presented clinical manifestations of complex partial seizures for several years. Overall, ^{99m}Tc-HMPAO SPECT detected rCBF changes in 95% of the patients, which were concordant, in location, to the abnormalities shown by CET in 85% of the patients. The extension of the abnormal perfusion demonstrated by ^{99m}Tc-HMPAO SPECT was, however, larger than the extension of abnormalities observed by CET in 40% of the patients. These patients were not operated on and, therefore, provide no insight into which of the technologies identified the seizure focus correctly. ^{99m}Tc-HMPAO SPECT was able to provide information about blood flow disturbances in deeper structures of the brain, such as basal ganglia (Table 1, Patients nos. 2, 3, 4 and 5, who had normal CT scans), which are not detectable by CET.

Combining ^{99m}Tc-HMPAO SPECT and CET data may be useful as a screening procedure in patients with medically refractory complex partial seizures avoiding in many cases invasive diagnostic measures in specialized centers for presurgical evaluation. A definitive assessment of the value of rCBF SPECT and CET as accurate tools for localizing and lateralizing the site of focal epilepsies is yet to be made. The role of these studies in an individual patient with complex partial epilepsy also remains to be validated in the future.

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