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PET and SPECT in epilepsy

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Epilepsy is one of the most frequent chronic neurological disorders, affecting 1–2% of the population. Patients with complex partial drug resistant episodes may benefit from a surgical treatment consisting in the excision of the epileptogenic area. Localization of the epileptogenic area was classically performed with video-EEG and magnetic resonance (MR). Recently, functional neuroimaging studies of nuclear medicine, positron emission tomography (PET) and single photon emission tomography (SPECT) have demonstrated their utility in the localization of the epileptogenic area prior to surgery. Ictal SPECT with brain perfusion tracers show an increase in blood flow in the initial ictal focus, while PET with 18F-DG demonstrates a decrease of glucose metabolism in the interictal functional deficit zone.

In this review, the basic principles and methodological characteristics of the SPECT and PET in epilepsy are described. The ictal SPECT injection mechanism, different patterns of perfusion based on the time of ictal, postictal or interictal injection are detailed and the different diagnostic sensitivities of each one of these SPECT are reviewed. Different methods of analysis of the images by subtraction and fusion systems with the MR are described. Similarly, the injection methodology, quantification and evaluation of the images of the PET in epilepsy are described. Finally, the main clinical indications of SPECT and PET in temporal and extratemporal epilepsy are detailed.

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PET y SPECT en la epilepsia

R E S U M E N

La epilepsia es uno de los trastornos neurológicos crónicos más frecuentes, afectando al 1–2% de la población. Los pacientes con crisis parciales complejas resistentes al tratamiento farmacológico pueden beneficiarse de un tratamiento quirúrgico que consiste en la extirpación de la zona epileptogénica. Clásicamente la localización de la zona epileptogénica se realiza con video-EEG y resonancia magnética (RM). Recientemente las exploraciones de neuroimagen funcional de medicina nuclear, la tomografía por emisión de positrones (PET) y la tomografía por emisión de fotón único (SPECT) han demostrado utilidad en la localización de la zona epileptogénica antes de la cirugía. La SPECT ictal con trazadores de perfusión cerebral demuestra un aumento del flujo sanguíneo en la zona de inicio ictal, mientras que la PET con 18F-DG muestra una disminución del metabolismo de la glucosa en la zona de déficit funcional interictal.

En esta revisión se describen los principios básicos y las particularidades metodológicas de la SPECT y la PET en la epilepsia. Se detalla el mecanismo de inyección de la SPECT ictal, los diferentes patrones de perfusión en función del momento de inyección ictal, postictal o interictal y se revisan las diferentes sensibilidades diagnósticas de cada uno de estos SPECT. Se describen diferentes métodos de análisis de las imágenes con sistemas de substracción y fusión con la RM. Del mismo modo, se describe la metodología de inyección, cuantificación y evaluación de las imágenes de la PET en la epilepsia. Finalmente se detallan las principales indicaciones clínicas de la SPECT y de la PET en la epilepsia temporal y extratemporal.

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Introduction

Epilepsy is one of the most frequent chronic neurological disorders, affecting 1.2% of the world population and its prevalence is 410 cases per 1000 inhabitants. In the United States the prevalence is 5 per 1000 inhabitants, affecting around 2 million people. The pharmacological treatment of epilepsy with one or several drugs achieves the seizure control in 60–70% of the cases. The remaining cases in which medication is not able to control the seizures constitute the group of patients with pharmacoresistant epilepsy. In these patients the seizures have a focal or partial origin in a limited, specific area of the cerebral cortex. These patients with partial pharmacoresistant seizures may benefit from surgical treatment which consists of surgical resection of the epileptogenic zone (EZ) defined as the cerebral tissue necessary and sufficient to generate an epileptic seizure. The success of surgery in epilepsy fundamentally depends on the correct presurgical planning which is usually based in the clinical seizure semiology and the EEG-video monitoring.
During admission, cortical dysplasias usually require complementary studies for diagnostic confirmation since the EEG and MR are usually not successful in locating these lesions. Some cerebral tumors of slow growth may generate epileptic seizures by themselves or by infiltration or irritation of the surrounding tissue. The most epileptogenic tumors are low grade astrocytomas, oligodendrogliomas, gangliogliomas, meningiomas in adults and dysembryoplastic neuroepithelial tumors (DNET) in children.

The last notable group of epileptogenic lesions is constituted by cavernoma-type vascular and arteriovenous malformations.

When MR localizes a structural lesion and the v-EEG coincides in locating the zone of seizure origin in the same region, the patients do not usually require other complementary neuroimaging studies to undergo surgery for the epilepsy. In addition, the presence of a lesion in the MR increases the success of the epilepsy surgery compared with patients with no lesion in the structural images. However, the percentage of surgical failure for epilepsy increases in the cases with suspicion of multiple foci, non-lesional MR, poorly defined cortical dysplasias or in those cases in which the lesion of the MR does not coincide with the localization of the EZ and the prediction of possible sequelae from the intervention.

Presurgical localization of pharmacoresistant epilepsy

For presurgical localization of the EZ, patients with pharmacoresistant epilepsy are admitted to the Epilepsy Unit where the presurgical assessment of the epilepsy is performed including the following diagnostic tests: clinical symptomatology, video-electroencephalogram (v-EEG), neuropsychological tests, psychiatric evaluation and neuroimaging studies. These tests help to define 6 cortical zones involved in the localization and extension of the EZ which are described in Table 1. During admission the antiepileptic medication is reduced or withdrawn to allow the appearance of a seizure which is registered with v-EEG. Analysis of the v-EEG during the interictal and ictal periods as well as the symptomatology of the seizure are essential to know the right or left hemispheric lateralization and lobar-frontal, temporal, parietal or occipital localization of the EZ. With surface electrodes the v-EEG is often not able to identify the EZ with sufficient precision. This occurs when the seizure originates in deep cerebral structures or when the seizure spreads rapidly. In this situation multiple electrodes are affected by the discharges making it difficult to decide where they initiate. In these patients it may be necessary to perform electroencephalogram (EEG) monitoring by the surgical placement of subdural or deep electrodes. This invasive procedure significantly increases the possibility of detecting the zone of ictal onset, the region in which the electrical seizures of the patient originate. However, invasive monitoring represents a series of risks among which the appearance of infection, epidural hematoma, headache and an increase in intracranial pressure are of note. In addition, for invasive monitoring to be useful it is essential to have a previously correct hypothesis as to the possible zones involved in the generation of the seizures. This hypothesis is what should guide the placement of the electrodes.

Morphological imaging in the presurgical localization of pharmacoresistant epilepsy

Morphologic neuroimaging with magnetic resonance (MR) has considerably reduced the need to implant intracranial electrodes due to its capacity to detect lesions acting as the EZ. However, conventional MR is inadequate for detecting subtle epileptogenic lesions which usually remain undetected in the usual T1-weighted and T2-weighted sequences. The MR should be acquired in high field equipment (1.5T or 3.0T), following a standard protocol for epilepsy including the 3D, T1-weighted, T2-weighted, FLAIR sequences and the ECHO gradient.

The cerebral lesion with the greatest epileptogenic capacity is mesial temporal sclerosis (MTS) which is the main cause of pharmacoresistant epilepsy in adult patients. This lesion consists in atrophy and gliosis of the hippocampus, and on MR it is manifested as a reduction in size and hyperintensity of the signal of the hippocampus in T2-weighted and FLAIR sequences (Fig. 1A). From a surgical point of view MTS is considered as a surgically treatable epileptic syndrome different from partial neocortical or extratemporal epilepsies. The natural evolution is known and does not require studies with invasive electrodes and may be surgically treated by temporal amebrolesional or selective amygdalohippocapctomy, achieving remission of the seizures in up to 80% of the cases. Focal cortical dysplasia and heterotopy are included among the malformations of cortical development (MCD) and are the first cause of pharmacoresistant epilepsy in infancy and the second/third cause in adults. These malformations are due to a disorder in the migration of the neuron levels in the embryonic stage and are shown as a subtle thickening of the gray matter and blurring of the margins between the gray and white matter. It is of note that the MR is normal in 40% of the cases of type 1 cortical dysplasia, and that the dysplastic region may be larger than the lesion detected on MR. Cortical dysplasias usually require complementary studies for diagnostic confirmation since the EEG and MR are usually not successful in locating these lesions.

Some cerebral tumors of slow growth may generate epileptic seizures by themselves or by infiltration or irritation of the surrounding tissue. The most epileptogenic tumors are low grade astrocytomas, oligodendrogliomas, gangliogliomas, meningiomas in adults and dysembryoplastic neuroepithelial tumors (DNET) in children.
Molecular imaging in the presurgical localization of pharmacoresistant epilepsy

Molecular imaging of the brain may be obtained by SPECT and PET. Both studies require previous injection of a radionuclide or radioligand which emit gamma photons in the case of SPECT and positrons in PET. According to the radioligand–administered images of blood flow, glycic metabolism or cerebral neurotransmission may be obtained. PET images have greater spatial resolution and more sensitivity to detect changes in cerebral tissue concentration of the radioligands than SPECT. Despite the increasing use of more PET equipment, the availability of the SPECT technique is greater and may be performed in all nuclear medicine departments.

Cerebral single-photon emission computed tomography

Tracers with the ability to cross the hematoencephalic barrier and fix themselves within the brain cell in proportion to the intracerebral blood flow are used in epilepsy. After the first pass through the brain, the radiotracer remains irreversibly fixed without redistribution. This particularity is essential for the ictal SPECT of epilepsy in which the tracer is injected during an epileptic seizure and remains fixed by the cerebral tissue during the initial seconds after injection and remains the same distribution for hours. These tracers may be hexamethylpropyleneamine oxime (HMPAO) or the ethylcysteine dimer (ECD), both markers having metastable technetium-99 (99mTc). Both tracers are small-sized lipophilic compounds which are transformed into a neutral charged hydrophilic compound on crossing the hematoencephalic barrier, being retained within the neuronal cell of the central nervous system.

Acquisition of images

It is recommended to use dual- or triple-head gamma cameras which allow high resolution images. Although low energy, high resolution, parallel collimators are appropriate, it is advisable to use convergent, fan beam type collimators to improve the resolution. The protocol to perform cerebral perfusion SPECT consists in the acquisition of a sequence of 120 or 128 images of 30 s each in 128 × 128 matrix with a pixel size of 3–4 mm.

The images may be reconstructed by filtered backprojection or iterative methods. It is not necessary to apply correction of attenuation, but if this is done it may be performed by the change method in the case of reconstruction by filtered backprojection or with the use of CT transmission images in which case the reconstruction should be performed by iterative methods. The images are presented in coronal, sagittal, frontal–occipital and temporal planes (parallel to the greatest axis of the temporal lobe according to a parasagittal plane).

Methodology of injection of the radiotracer (interictal and ictal single-photon emission computed tomography)

For interictal SPECT 740 MBq 99mTc-HMPAO or 99mTc-ECD are injected intravenously in the forearm of the patient in a resting position with a seizure-free period of time greater than 24 h. The antiepileptic medication is usually not withdrawn for the SPECT since it may increase the risk of presenting seizures, although it is known that some antiepileptics such as barbiturates diminish cerebral blood flow.

For the ictal SPECT the dose of the tracer (ECD or stabilized-HMPAO) labeled with 99mTc should be prepared at the head of the bed of the patients in a room in the epilepsy unit. The syringe should be correctly sealed and connected to the patient with an intravenous line catheter. The patients should remain under constant

Fig. 1. Patient with complex partial seizures of right temporal lobe origin. (A) MR in T2-weighted sequence demonstrating atrophy and right hippocampus hyper-signaling; (B) interictal SPECT with 99mTc-HMPAO showing right anterior temporal lobe hypoperfusion; and (C) ictal SPECT showing intense and extensive increased perfusion of the tracer in the right temporal lobe.

localization of the v-EEG. It is in all these situations in which functional neuroimaging studies such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) may provide fundamental additional information for localizing the EZ.

Epilepsy refractory to pharmacological treatment constitutes 25–30% of the cases of epilepsy in children, and it is often associated with other neurological disorders or even psychomotor retardation. In infancy, the localization of the EZ before surgery is a diagnostic challenge since the neuropsychological tests are not as useful and the sensitivity of the MR is lower. This is because extratemporal epilepsy predominates in children, and the main cause of epilepsy is cortical dysplasia, and cerebral immaturity diminishes the contrast between the gray and white matter, hindering the visualization of the cortical lesions. However, surgery should not be delayed since when it is performed in well selected cases and thanks to the cerebral plasticity, surgery for epilepsy achieves seizure remission in 60–70% of children.

In view of the limitations of the clinical, neuropsychologic and structural imaging data, functional neuroimaging tests have a relevant role in localizing the EZ.
supervision by the EEG technician who is pending the detection of the clinical onset or EEG of an epileptic seizure. On initiation of a seizure, the tracer should rapidly be injected as a bolus. The volume to be injected should be adapted to the decay of the radiotracer and the dead-space needle/syringe to guarantee a dose between 20 and 25 mCi during the 8 h in which the tracer is usually available beside the patient.

Injection of the radiotracer during a seizure is the most critical part of performing ictal SPECT. Manual injection of the radioactive tracer requires a person to remain at bedside during long periods which usually delays the injection of the tracer, diminishing the diagnostic yield of SPECT. Some centers have automatic injection systems of the dose of the SPECT thereby facilitating the methodology, reducing the injection time, avoiding the manipulation of radioactive products and adjusting the volume to be injected taking the decay of the 99mTc into account and ensuring injection of the indicated dose.13-15

The in vitro instability of 99mTc-HMPAO makes it less appropriate for ictal SPECT, having to remain next to the patient up to a maximum of 3 h while awaiting a seizure. The greater stability of 99mTc-ECD allows tracer availability for more than 8 h in addition to having greater radiochemical purity and guarantees better quality images with less extracerebral activity.16 However, it has been described that the ictal increased uptake of 99mTc-HMPAO is greater than that of 99mTc-ECD, thereby providing greater sensitivity.17

Once the radiotracer has been injected the patient must be stabilized. Fast acting antiepileptic medication may be administered with, for example, 5–10 mg of midazolam, prior to the acquisition of ictal SPECT images. The time between the injection of the tracer and image acquisition is not well established. The images should be acquired within 3 h post-injection, although it is most convenient to do this in the first hour to avoid worsening of the image due to decay.

Interpretation of the images and cerebral perfusion patterns

In the visual evaluation interictal SPECT shows an area of hyperperfusion in the zone of functional deficit of the EZ (Fig. 1B). However, the hyperperfusion is not specific of the EZ since other cerebral lesions may produce zones of hyperperfusion in the cerebral SPECT. Moreover the sensitivity of interictal SPECT to localize the EZ is low and is often normal. Thus, the main application of interictal SPECT is that of having a basal study to compare the changes presented by ictal SPECT and facilitate interpretation.18

Ictal SPECT may indicate the zone of seizure origin. The increase in neuronal activity triggered by the epileptic seizure carries an increase in neuronal metabolism as well as in regional blood flow which is manifested as focal hyperuptake in the SPECT (Fig. 1C). The pattern of hyperperfusion may change or extend toward other zones of the brain distant from the zone of seizure onset as the epileptic seizure propagates toward other cerebral regions. Thus, because of the low temporal resolution of SPECT and depending on the immediacy of the tracer injection from the onset of the seizure, SPECT hyperperfusion contains the zone of ictal onset and/or the main pathways of propagation. Another usual finding is the presence of areas of hyperperfusion around the area of hyperperfusion. This adjacent hyperperfusion has an uncertain origin which has been related to the phenomenon of vascular steal or inhibition of the propagation. A determining factor is the cause of delay in tracer injection particularly if injected when the epileptic seizure has finished.

In this post-ictal situation the hyperperfusion progressively transforms into hypoperfusion, although the changes of perfusion of post-ictal SPECT based on time are not well established. When the EZ is localized in the medial structures of the temporal lobe, early post-ictal SPECT (tracer injection within the first 60–100 s after the initiation of the seizure) usually shows extensive and intense temporal hyperperfusion similar to that of ictal SPECT. If the injection is made after the first 60–100 s after ictal onset, the temporal hyperperfusion diminishes, especially in the lateral temporal lobe, but the mesial temporal lobe remains with hyperuptake. If the injection is performed later at 2 or 3 min after the end of the seizure extensive and diffuse hypoperfusion is visualized.19 This is because the epileptic seizure is a dynamic process in which the SPECT only shows the changes in perfusion at a specific moment of the process.

Therefore, to assess ictal SPECT it is essential to know whether the injection was ictal or post-ictal and thus, the time from the onset of the seizure and the injection of the tracer should be noted. Visual evaluation of ictal SPECT images and their comparison with those of interictal SPECT visualizing homologous slices is a laborious and complex task. Thus, in the last year software that will help to more precisely and simply carry out this task have been developed. These programs register both the ictal and interictal SPECT studies creating an image which demonstrates the differences between the two studies, overlaid with the MR image of the same patient, co-registered prior to the SPECT studies. This widely used methodology which is known as subtraction of ictal SPECT coregistered to MRI (SISCOM) was described by O’Brien et al.20 in 1998. Since then, programs such as the Analyze,21 ISAS (Bioimage Suite)22 or FocusDET,23 which allow this technique to be performed, have appeared and are being commercialized to this end. Analyze and Bioimage Suite is a general package for the processing of images while FocusDET is oriented to the presurgical evaluation of epilepsy.

The SISCOM Analysis plug-in of FocusDET www.ciber-bbn.es/ focusdet is a new tool to perform the SISCOM methodology in a single work setting. The workflow of this platform is composed of the following steps: (1) importation of the studies in DICOM format from a PACS server; (2) registry of the ictal and interictal SPECT by rigid transformation using the local coefficient of correlation as cost function24; (3) normalization of the intensity of the SPECT images and production of the image subtraction; (4) generation of a brain mask from segmentation of the MR Image25 to diminish artifacts due to extracerebral activity; (5) registry of the SPECT studies to the structural MR image by rigid transformation of multiresolution26 and finally; (6) fusion of the focus with the structural MR image, showing only those values of the image subtracted with an intensity greater than a determined number of standard deviations over the mean (usually 1.5 or 2 standard deviations). Clinical performance of single-photon emission computed tomography in temporal lobe epilepsy

Ictal SPECT may demonstrate a reduction in cerebral blood flow related to the EZ in 50–70% of the complex partial seizures of the temporal lobe.18 This elevated variability depends on the methodology used since it is not usually observed in equipment with low resolution due to the partial volume effect which occurs in a small size structure.

Ictal SPECT detects an increase in cerebral blood flow in the EZ in more than 90% of the patients with temporal lobe seizures.27,28 Although the lesion causing the seizure is a sclerosis of the hippocampus, ictal SPECT shows a very intense and extensive increase in perfusion which usually includes all the anterior pole of the temporal lobe. This may be explained by the propagation of the seizure or by the effect of partial volume due to the limited resolution of the SPECT.

With the delay in the time of the injection the sensitivity of the SPECT to adequately detect temporal hyperperfusion diminishes from 80% in the early post-ictal SPECT to less than 60% in the delayed study.29,30
The most determinant factor for correct diagnostic interpretation of ictal SPECT is that the injection of the tracer should be very rapid and as close as possible to ictal onset. Delay in injection produces more extensive, less localizable, hyperperfusion by the propagation or even the appearance of several foci of increased activity that may even lead to false localizations.

Clinical performance of single-photon emission computed tomography in extratemporal epilepsy

The diagnostic precision of SPECT in neocortical epilepsy is significantly diminished. The sensitivity of interictal SPECT to localize hypoactive areas in the EZ is 15.30% which is why it does not usually provide information to localize the EZ.

In extratemporal epilepsy ictal SPECT is the diagnostic imaging technique with the highest yield in the localization of the zone of seizure onset with a sensitivity of around 66%.[33,34] However, due to the briefness of extratemporal seizures, it is difficult to obtain an ictal SPECT, and in many cases, only post-ictal SPECT can be achieved, being of scarce utility in extratemporal epilepsy, with a sensitivity of 20–50%.[37] Post-ictal SPECT in neocortical epilepsy may be normal or show one or several zones of hypopuftake which do not precisely localize the zone of ictal onset.

O’Brien was aware of the difficulties in the interpretation of SPECT in extratemporal epilepsy and demonstrated that the SISCOM methodology increased the diagnostic sensitivity of ictal SPECT from 40 to 88%, and increased the specificity and improved the anatomical localization of the zone of seizure onset to overlay the image of ictal–interictal subtraction on the MR of the patient (Fig. 2). These authors indicated that the probability of localizing the zone of ictal onset with SISCOM is greater than that of v-EEG and MR,[30] and that complete resection of the increased focal activity of the SISCOM improves the prognosis of surgery.[35] In our experience SISCOM completely changes the interpretation of ictal SPECT, and it is an essential tool for the cerebral SPECT in epilepsy. The SISCOM often detects active foci not detected in the visual assessment of the ictal SPECT. However, it should always be retrospectively checked that the focal zone obtained by SISCOM is visualized as increased uptake in the ictal SPECT to rule out an artifact. This situation of negative ictal SPECT and positive SISCOM is especially evident when 99mTc-ECD is used as the radiotracer. With 99mTc-ECD the ictal increase in uptake is usually of lesser intensity than with HMPAO. However, the quality of the images and the lower extracerebral activity of SISCOM with 99mTc-ECD present fewer artifacts, thereby highlighting small foci of increased uptake not detected in the visual analysis.

Clinical applications of SISCOM in mesial temporal lobe epilepsy

• In patients with clinical symptomatology which is not typical of mesial temporal lobe epilepsy.

• In patients with a critical pattern in the EEG which is not characteristic of mesial temporal lobe epilepsy.

• In patients with independent bilateral temporal lobe seizures the ictal SPECT may show increased uptake in the temporal lobe which produced the seizure at the time of the injection.

• In patients with 2 or more lesions in the MR (dual pathology). In this situation the ictal SPECT is the only imaging study which is able to demonstrate which lesion is responsible for the epilepsy.

• In patients with non-lesional epilepsy: despite the new 3T MR equipment and the use of specific sequences, 20–30% of patients with temporal lobe epilepsy present a normal MR.[36] In these cases with suspicion of mesial temporal lobe epilepsy and negative MR, the ictal SPECT is of great utility for confirming the temporal lobe origin of the epilepsy.

• Since the behavior of neocortical temporal lobe epilepsy is similar to that of extratemporal epilepsy it is reviewed in the next section.

Clinical applications of SISCOM in extratemporal epilepsy

• In suspicion of neocortical extratemporal epilepsy. Increased uptake of ictal SPECT in neocortical epilepsy is usually less extensive and intense than in mesial temporal lobe epilepsy making SISCOM a more necessary tool in extratemporal epilepsy.

• In non-lesional epilepsy. 25–40% of patients with epilepsy at an adult age have a normal or non-lesional MR and 20–40% of focal cortical dysplasias do not show alterations in the MR.[37] In both cases, SISCOM may be the only imaging study which allows localization of the EZ and confirms the data of the v-EEG.

• During discordance among studies. Won et al.[38] found that 30–40% of the 118 patients included in their study showed discordances in the localizations of the possible EZ by MR and v-EEG. Thus, one of the greatest clinical applications of SISCOM is to demonstrate whether a lesion detected in the MR is really an epileptogenic lesion or is an incidental lesion not related to the epilepsy.

• The MCD are a frequent cause of epilepsy, especially in childhood. It also seems that there is no clear relationship between the real extension of the dysplasia and the MR image. Thus, SISCOM may help to more precisely delimit or confine the zone of seizure onset in the dysplastic territory while also allowing the detection of ictal activity in negligible cortical dysplasias or which are very subtly visualized in the MR. O’Brien et al.[39] demonstrated that ictal SPECT with SISCOM localized the ictal zone in 19/22 patients with dysplasias (86%) and in 8/10 cases with normal MR.

• In extensive, multilobar or bilateral lesional epilepsy, neocortical syndromes or MCD. In patients with extensive or multifocal cerebral lesions SISCOM may demonstrate ictal activity in a more limited zone within the structural lesion. This allows mapping of a more limited cerebral region with intracranial electrodes prior to surgery.
• During reappearance of seizures in previously operated patients presenting non-localizable residual lesions. In patients previously operated for tumors, with dysplasia or after traumas, who already present a residual structural cerebral lesion, SISCOM may demonstrate an increase in perfusion adjacent to the lesion of residual encephalomalacia.

• Prior to the placement of subdural electrodes to reduce the extension of the area to cover and minimize the risks of surgery.

• In infantile epilepsy. Almost all the difficulties described above occur in infantile epilepsy. The seizures are generally extra-territorial, of short duration and the most common pathology is dysplasia. Our SISCOM results in children and those described in the literature are excellent, with imaging studies presenting the greatest diagnostic yield. In a series of 54 children the sensitivity of MR was 39% and that of SISCOM was 76%. It is of note that in the 33 cases with a normal MR or which did not localize extensive or residual lesions, the SISCOM localized the EZ in agreement with the v-EEG in 57% of the cases.

Positron emission tomography with 18F-FDG

Methodology: preparation, injection, acquisition and processing

In epilepsy PET is only used in the interictal phase and may be done in the outpatient setting. It is therefore a methodologically simpler and more feasible study for patients evaluated in epilepsy units which do not have a nuclear medicine department. The tracer commonly and routinely used in the clinical setting is 18-fluoro-2-deoxyglucose (18F-FDG). Other tracers of gababergic benzodiazepinic neuroreceptors such as 11C-flumazenil or serotoninergic receptors such as 11C-alpha-methyl-triptophan are in the experimental phase and are occasionally used and are therefore not the object of this review which is only focused on the clinical use of 18F-FDG. This glucose analog is transported to the brain tissue via the cerebral blood flow, but its distribution reflects the intracerebral metabolism of glucose.

In accordance with the recommendations of the European Association of Nuclear Medicine, the preparation of the patient requires 4 h of fasting to maintain optimum, stable glycemia and does not advise injection of the dose in a state of hyperglycemia (>160 mg/dl) since the cerebral uptake of the tracer and the contrast between the gray and white matter diminishes in this situation. The acquisition of images should not be initiated before 30 min after injection and should preferably be acquired at 30–60 min. During this period of time the patients should remain resting in a silent, dimly lit room. To improve patient comfort during the study and minimize exposure to radioactivity, the patient is instructed to void the bladder before and after the study.

The recommended dose of 18F-FDG in adults with acquisitions in 3D mode is of 125–250 MBq. In children the dose should be adjusted according to the recommendation of the EANM.

The 2 details of PET in epilepsy are the need to do continuous EEG registry during the uptake of the tracer and the frequent need for anesthetic sedation, particularly in pediatric studies. Anesthetic sedation should be initiated immediately before the acquisition of the PET and always 30 min after the injection of the 18F-FDG to avoid interferences with the uptake of the radiotracer. This is routinely performed in children from 6 to 7 years of age and in selected cases of patients of older ages.

Continuous EEG registry is performed to confirm the absence of ictal activity during the uptake of 18F-FDG and thereby ensure that it is an interictal PET. EEG registry should be acquired continuously before the injection of 18F-FDG and should be maintained at least 20 or 30 min after the injection. It is not strictly necessary in patients with a low frequency of seizures or in those whose seizures are clinically detectable and recognizable by patients and relatives. However, this methodology is mandatory in patients with an elevated frequency of seizures or with subclinical seizures, both of which are very usual at pediatric ages. The presence of seizures during the uptake of 18F-FDG may lead to an ictal PET with a focal or diffuse increase in uptake in a region, lobe or hemisphere. Unawareness of this situation may produce false lateralizations of epilepsy since an incorrect normalization may be interpreted as ictal hypermetabolism such as normal cerebral uptake and the cerebral regions with normal uptake may be considered as false hypometabolism.

The acquisition of PET should be performed in 3D mode to increase the count statistics and reduce the dosimetry. It is also necessary to acquire a CT or a transmission scan for correction of attenuation. The reconstruction is done with iterative methods with random corrections of events, dispersion and attenuation of photons.

Interpretation of the images

The most characteristic finding of interictal PET in epilepsy is a regional reduction of the uptake of 18F-FDG (hypometabolism) which presumably reflects a focal dysfunction of the cerebral activity in the epileptogenic tissue. The cause of interictal hypometabolism of 18F-FDG is still not clear, but it seems to be related to a loss of neuronal cells and a decrease of synaptic impulses due to the constant generation of anomalous electric activity. Thus, the hypometabolism of PET is not only limited to localizing the epileptogenic foci, but it is usually more extensive and overpasses the true EZ. The hypometabolic region usually covers the zone of ictal onset, the zones of ictal propagation and of post-ictal depression which may even be distant from the zone of ictal onset. This is why the use of PET for defining the margins of surgical resection is controversial.

Clinical evaluation of PET with 18F-FDG is performed by visual inspection of the images in slices parallel to the frontocerebral, coronal, sagittal and temporal axes, and, in our experience it is preferable to assess the images with a polychromatic color scale. Methods applying tests of statistical comparison between the cerebral metabolic activity of the image of the subject and that of a database of healthy subjects or which evaluate the asymmetry between the cerebral hemispheres may also be used.

For the statistical comparison of the study of a patient and a database, previous pre-processing of the image of the patient is first necessary, consisting in spatial normalization to a standard space, a normalization of intensity and smoothing. The spatial normalization consists in applying a geometric transformation (rotations, translations and deformations) to the image of the patient which adjusts the image to a standard stereotactic space. To do the spatial normalization a reference PET image is required in the coordinates of this standard space denominated template image. On the other hand, the mean global level of cerebral metabolism varies among different subjects and, to a lesser extent, in the same subject with the passage of time thereby making it necessary to make a normalization of intensity. Finally, and prior to the statistical analysis, the images must undergo a smoothing mainly for the reduction of statistical noise using a Gaussian image filter defined by the full width at half maximum (FWHM) parameter. These same operations have previously been performed in all the images of the database for voxel to voxel comparison. The statistical comparison consists in applying a T-test for independent samples in each voxel. For this comparison it is hypothesized that the variance associated with the subject in each voxel is the same as that of the database for this same voxel. This is necessary on comparing 2 groups, one of which is made up of a single subject, the patient. Comparisons of each voxel in the image are made, leading to the appearance of numerous positive results of the test due to chance. However, it is difficult for the
Fig. 3. Cerebral PET with $^{18}$F-FDG showing extensive hypometabolism of the left temporal pole in a patient with left mesial temporal sclerosis.

voxels in which this occurs to be grouped. For this reason only the possible groups of voxels with significant results in the comparison should be considered as positive results of the comparison test. In general, the criteria used to accept regions with significant changes of regional cerebral metabolism are, on one hand, the statistical significance ($p < 0.001$ or $p < 0.005$) and, on the other hand, the extension of the contiguous voxels ($k \geq 100$). For the interpretation of PET of epilepsy the test should be applied with an adequate contrast to detect zones of lesser metabolism in the patients compared to the controls since hypometabolic areas which may be responsible for the epileptic seizures are sought.

The statistical analysis is usually performed with the Statistical Parametric Mapping (SPM) package which contains numerous image processing tools.

Clinical performance of positron emission tomography in mesial temporal lobe epilepsy

The sensitivity of PET in temporal lobe epilepsy is 80–90%.\textsuperscript{50,51} Temporal lobe hypometabolism may be restricted to the medial structures or extend toward the temporal pole probably because the temporal neocortex is involved in mesial temporal lobe epilepsy.\textsuperscript{52} Thus, PET cannot usually differentiate mesial temporal lobe from lateral epilepsy (Fig. 3). On the other hand, the metabolic integrity of the temporal pole confirmed with PET may support a more restrictive resection with selective resection of the hippocampus and the amygdala versus classical anterior temporal lobectomy.\textsuperscript{53} Moreover, recent studies using quantitative methods have demonstrated that in mesial temporal lobe epilepsy PET may show regional hypometabolism in the frontal, parietal, insula and ipsilateral cortex as well as in the contralateral temporal lobe.\textsuperscript{46} This pattern may represent the epileptic network involved in the propagation of the seizure and be responsible for the clinical symptomatology.

Clinical performance of positron emission tomography in extratemporal epilepsy

The sensitivity of PET in extratemporal epilepsy ranges from 45 to 92%.\textsuperscript{54} The greatest clinical yield is observed in patients with non-lesional epilepsy since the hypometabolic lesion of the PET may be the only imaging technique which confirms the EEG findings, being fundamental for surgical decisions in these cases (Fig. 4). The quantification techniques described in the previous section as well as PET/MR co-registry may increase the capacity of detection on demonstrating small sized lesions not detected in the visual inspection of the images\textsuperscript{55,56} (Fig. 5). On the other hand, one of the limitations of PET in epilepsy is that the regional hypometabolism is not specific of epilepsy and other “non-epileptogenic” lesions may produce a hypoactive image. Thus, when the MR shows a structural lesion with no clear relationship with the EZ such as ischemic lesions or encephalomalacia, PET does not usually provide additional information on demonstrating an absence of metabolism in the structural lesion. Despite this, the PET provides additional information in the presurgical localization in two thirds of the patients, modifies the surgical decision in 50–70% of cases and is decisive in 16% of the cases.\textsuperscript{57}

Fig. 4. Nine-year-old patient with malformation of the development of the left frontal cortex and normal MR. PET/MR image shows marked hypometabolism in the superior frontal, cingulum and left supraorbital cortex which delimit the focal cortical dysplasia.
Clinical applications of positron emission tomography in mesial temporal lobe epilepsy

- In non-lesional epilepsy. Despite the elevated sensitivity of MR in MTS (97%), 16% of the patients with temporal lobe epilepsy have a normal MR. In these patients PET lateralizes the lesion in 80% of the cases and has a relevant role for surgical decisions on being the only imaging study to demonstrate dysfunction of the temporal lobe. In addition, the prognosis of surgical success in patients with a normal MR and positive PET (75%) is equal to that of patients with MTS in the MR (78%).
- To show discrepancy between the v-EEG and MR. PET is useful in patients with MTS in the MR and v-EEG registry showing frontal or bi-temporal ictal activity suggestive but not conclusive of propagation of the focus of temporal ictal onset. It is also useful in cases with MTS but with ictal clinical symptoms which are not common to temporal lobe epilepsy or suggest a possible extratemporal origin.
- In patients with dual disease due to the presence of MTS and another incidental neocortical lesion in the MR. In these cases, the hypometabolism of PET in a temporal pole may confirm the temporal EZ.

Clinical applications of positron emission tomography in extratemporal epilepsy

- Non-lesional epilepsy. Patients with no structural lesion in the MR are usually ruled out for surgery since the results of the surgery are less favorable. In the absence of SISCOM, PET may be the only imaging test to inform about the possible localization of the EZ and may be used to establish the surgical hypothesis with or without intracranial electrodes.
- Cortical dysplasia. MR has little capacity to detect cortical dysplasia, being negative in 40% of type I dysplasias and 10% in type II dysplasias in which it also has difficulty in delimiting the margins of the lesion. The sensitivity of PET in dysplasias varies from 70% to 90%, and its yield increases with the fusion of PET with the MR of the patients or with SPM quantification techniques.
- In the placement of intracranial electrodes. The hypometabolic territory of PET may be used to place the intracranial electrodes in a cerebral region more precisely, reducing the extension to study and thereby possibly decreasing the morbidity of the technique.
- To evaluate the regional cerebral functional capacity. In patients who are candidates for surgical resection, PET with $^{18}$F-FDG allows evaluation of the functional integrity of the remainder of the brain. This is fundamental to delimit the surgical resection and predict cognitive status after the intervention, which depends on the functional integrity of the non-resected cortex.
- In infantile epilepsy. Extratemporal epilepsy predominates in children and MR shows a lower yield because of the lesser contrast between the white and gray matter and the elevated frequency of cortical dysplasia. Delay in surgery worsens the prognosis since the repetition of seizures deteriorates correct psychomotor development in these children. At this early age in which the MR is usually normal, surgery in epilepsy is more advantageous due to the great cerebral plasticity. In these circumstances PET may support the surgical decision by demonstrating a hypometabolic zone in concordance with the possible EZ. Several studies support the elevated sensitivity of PET in infantile epilepsy and our own results in a group of 31 children with non-lesional epilepsy showed a PET sensitivity equal to 67% to localize the EZ. The study by Ollenberger et al. demonstrated that PET changed the clinical management of more than half of the pediatric patients who were candidates for surgery. Considering the simplicity of the technique and its elevated clinical performance we believe the routine use of PET with $^{18}$F-FDG to be justified in children with infantile epilepsy who care candidates for surgery.
Summary: multimodality

Presurgical localization of the possible EZ is a complex task which should be individualized in each case and discussed following a multidisciplinary modality in epilepsy units. In cases in which the clinical symptomatology, the ictal and interictal EEG and the MR are concordant in the localization of the possible EZ, the surgical approach is safe and provides good results. Unfortunately, some of these studies are not conclusive or disagree in an elevated percentage of cases. In this situation, nuclear medicine studies play a decisive role. The sensitivity of SISCOM may be somewhat greater than that of interictal PET and it is also the only imaging study to demonstrate the zone of ictal onset. On the other hand, PET is less complex and may be performed in an outpatient setting. Both studies share indications and in the absence of guidelines or a clear algorithm it is difficult to specify which should be used in each case. Moreover, during the admission of the patient in the epilepsy unit, it is difficult to predict which study will provide the greatest yield if all the studies are not available. It seems that a positive PET with a normal MR is diagnostic in non-lesional epilepsy. In cases in which all the studies are not available. It seems that a positive PET with a normal MR is diagnostic in non-lesional epilepsy. In cases in which the MR shows a chronic or non-localized residual lesion, SISCOM has a greater yield. However, the two studies are often obtained in the same patient and fusion of all the imaging studies over the MR of the patient usually provides valuable information for surgical decisions which may even avoid the need to implant subdural or intracranial electrodes.

Points of interest

1. Patients with partial pharmacoresistant seizures may benefit from surgical treatment which consists in surgical resection of the EZ.
2. The EZ is the cerebral cortical region responsible for generating epileptic seizures. By definition, its surgical resection or complete disconnection is sufficient to eliminate the seizures.
3. Interictal SPECT shows hypoperfusion in the zone of functional deficit of the EZ. The hypoperfusion is not specific and the sensitivity to localize the EZ is low. It is essential to interpret the changes in perfusion of the ictal SPECT and the SISCOM.
4. Ictal SPECT shows an increased uptake due to an increase in blood flow in the zone of seizure onset.
5. In post-ictal SPECT the increased uptake is progressively transformed in decreased uptake.
6. The most determinant factor for the correct diagnostic interpretation of ictal SPECT is that the injection of the tracer must be rapid and as close as possible to the ictal onset.
7. The methodology to perform the subtraction of the ictal with the interictal SPECT co-registered with the MR of the patient (SISCOM) increases the sensitivity of the ictal SPECT and improves the anatomical localization of the zone of seizure onset.
8. Interictal PET with 18F-FDG shows increased uptake due to a reduction in the metabolism of glucose in the zone of functional deficit.
9. Clinical evaluation of cerebral PET with 18F-FDG is performed by visual inspection of the images although the PET-CT co-registration improves the anatomical localization.
10. Analysis of the PET with methods applying tests of statistical comparison between the cerebral metabolic activity of the image of the subject and that of a database of healthy subjects may help to confirm small sized lesions.

Conflict of interests

The authors declare no conflict of interests.


