POSITRON EMISSION TOMOGRAPHY IN PRESURGICAL LOCALIZATION OF EPILEPTIC FOCI

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2002
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1. INTRODUCTION

Approximately 0.5% to 1.0% of the population suffer from some form of epilepsy, and in 15%-20% of cases the seizures are intractable, i.e., refractory to medical treatment with anticonvulsants. Epilepsy is particularly devastating in the pediatric age group. Frequent or prolonged seizures have been causally implicated with regard to brain dysfunction and maldevelopment in humans and animals (1-4). Therefore, treatment of intractable epilepsy is aimed at both seizure control and, in infants and children, allowing for normal cognitive development.

1.1. Presurgical evaluation in medically refractory epilepsy

When seizures cannot be controlled with medication, surgical treatment may be considered. Epilepsy surgery is increasingly being performed as a result of improved neurosurgical techniques, improved intensive care, better knowledge of developmental brain plasticity, improved preoperative evaluation (particularly neuroimaging), and general recognition that a progressive epileptic encephalopathy should be avoided. However, the outcome of epilepsy surgery with respect to seizures widely varies depending upon the type of epilepsy and operation performed, and the ultimate results remain far from optimal. In adults, the most common and successful procedure performed is a standard temporal lobectomy, which yields seizure-free outcome in about 2/3 of the cases (5,6). Recent advances in structural and functional neuroimaging allow non-invasive presurgical detection of hippocampal sclerosis (the most common pathological substrate of temporal lobe epilepsy) with a high accuracy. The success rate of cortical resection in epilepsies of neocortical origin, especially those originating from extratemporal regions (which are especially common among children), continues to be disappointing. In a review of surgical outcome from 10 epilepsy surgery centers worldwide (5), only 45% of 805 patients undergoing extratemporal cortical resections became seizure free. The success rate is even worse when no structural lesion can be identified on MRI (7-9). In a series reported from the Mayo Clinic, Schiller et al. (9) reported that of the patients with no detectable
MRI lesion and who were subjected to chronic intracranial EEG monitoring, only 22% became seizure free after surgery.

The most important aspect of presurgical evaluation is the identification of a discrete epileptogenic region (i.e. the area of brain necessary and sufficient for generation of habitual spontaneous seizures [10]), which can be surgically resected without causing an unacceptable loss of neurological function, and which will lead to complete seizure control. This region, however, is theoretical because its boundaries can be only assumed, but not directly defined, from complementary structural (epileptogenic lesion delineated by structural neuroimaging) and functional information (obtained from EEG and functional neuroimaging data) derived from the epileptic brain. The decision to recommend epilepsy surgery is based on convergence of data from an analysis of seizure semiology, scalp interictal and ictal EEG, anatomical and functional neuroimaging, and neuropsychological evaluation.

When these data are nonconvergent, the patient is either not considered further for surgery or may be subjected to invasive intracranial EEG monitoring with depth or subdural electrodes. Chronic intracranial EEG evaluation remains the “gold standard” in defining the boundaries of the epileptogenic region to be resected in order to achieve complete seizure control. Although there is a general agreement that the region of ictal onset is the most reliable EEG criterion for defining the epileptogenic region, delineation of this zone is not always successful even when invasive monitoring techniques are utilized. This is especially true for neocortical epilepsies where the localizing value of surface EEG is commonly poor and the reliability and accuracy of intracranial grid EEG monitoring is highly dependent on other localizing information. It is also compromised by the spatial limitation of the electrode coverage (11). In fact, subdural EEG recording is often unreliable to localize seizure onset in the absence of other localizing information (9, 12-14).

Successful localization is poor without imaging clues and a high-risk of sampling error exists especially in frontal lobe epilepsy (15), where a widespread distribution of the epileptogenic brain tissue responsible for the patient's habitual seizures can also contribute to a false or missed localization (16). Because intracranial EEG recording carries a 1-4% risk of significant morbidity and possible mortality (15), it is appropriate only when reliable conclusions cannot be obtained by less invasive methods.
Due to suboptimal results of resective surgery, and the above-mentioned risks, limitations and pitfalls of invasive EEG techniques, the quest for new (structural and functional) neuroimaging methods is well justified. Development and clinical application of such methods is aimed at replacement of invasive EEG recording or providing a reliable guide for electrode coverage when invasive EEG is inevitable.

1.2. Neuroimaging can improve localization of epileptic brain regions

Unlike the limited sampling available with intracranial EEG monitoring, neuroimaging allows assessment of the entire brain in order to define the location and extent of all abnormal regions. Both structural and functional neuroimaging techniques are valuable in the localization of potentially epileptic brain regions.

1.2.1. MRI in presurgical localization

During the past decade, development of MRI provided a new insight in the variety of structural brain abnormalities located in epileptogenic brain regions. Volumetric studies of the hippocampus and amygdala proved to be very sensitive in lateralizing the epileptogenic region, as defined by extracranial and intracranial EEG in temporal lobe epilepsy of medial temporal origin (17,18). A strong relationship between the degree of hippocampal volume loss and the severity of hippocampal sclerosis has been reported (19). Combination of volumetric MRI and proton magnetic resonance spectroscopic imaging (detecting and quantifying focal neuronal damage or dysfunction based on reduced signals from the neuronal marker $N$-acetylaspartate) was reported to further increase the sensitivity of MRI in temporal lobe epilepsy.

In neocortical epilepsy, recent applications of inversion recovery techniques, high resolution MRI imaging with thin slices, and multiplanar reconstruction have improved the sensitivity of MRI for detecting cortical dysgenesis (20-23), which has been reported in up to 30% of epilepsy surgery specimens and is believed to represent the central pathologic substrate responsible for seizures (24). However, even with the high spatial resolution and sensitivity of MRI, very small regions of disordered neuronal migration (called microdysgenesis) may not be detected. This entity has been reported in up to 43% of temporal lobe specimens (25), and it has been often found in children with intractable infantile spasms who underwent successful cortical
resection (26). It has been also increasingly recognized that epileptogenic cortical regions can variably extend beyond the visible lesion (10). Further, the presence of unsuspected dual pathology, i.e. co-existence of an epileptogenic cortical lesion and hippocampal sclerosis, can also lead to surgical failure. In such cases, functional neuroimaging can be applied to further delineate the epileptic cortex.

Nevertheless, the application of quantitative MRI techniques has reduced the number of patients requiring invasive, prolonged, and expensive EEG monitoring in the presurgical evaluation of refractory temporal lobe epilepsy. In neocortical epilepsies, which are particularly common in young patients, however, structural imaging (even with the most sophisticated techniques applied) often does not provide sufficient localizing information.

1.2.2. Functional neuroimaging in the study of human epilepsy. The application of functional neuroimaging, in intractable epilepsy has recently focused on those patients with normal structural neuroimaging (MRI), those with multifocal MRI abnormalities, and those with focal MRI abnormalities associated with discordant electro-clinical findings. Among various functional neuroimaging techniques, magnetic resonance spectroscopic imaging, functional MRI, magnetic source imaging, single photon emission tomography (SPECT), as well as positron emission tomography (PET) with different radiotracers have all been applied to assist localization of epileptic foci. Functional neuroimaging performed in ictal or interictal states of epilepsy can lead not only to improved detection of epileptic brain regions, but also represents a powerful research tool for better understanding pathophysiology of human epilepsy.

The present study focuses on the application of PET in intractable epilepsy, with a special emphasis on epilepsies of neocortical origin. These studies were carried out to address both pathophysiological aspects of human epilepsy and clinical applications of PET in the presurgical localization of epileptic areas. In order to achieve these objectives, information provided by PET was interpreted in the context of cerebral structural (MRI) and electrophysiological (interictal and ictal EEG) findings and also in conjunction with clinical characteristics of intractable epilepsy.

1.3. PET in intractable epilepsy
PET is a noninvasive imaging method, which can be used to image and quantify local biochemical processes within the brain and other organs, and employs the principles of tracer kinetics (27). The tracers used in PET are labeled with short-lived isotopes, which emit positrons that collide with surrounding electrons resulting in annihilation of both particles and the release of paired high-energy (511 keV) photons. These photons travel in opposite directions and can be recorded by multiple pairs of oppositely situated detectors that constitute the PET camera (28, 29). The coincidence detection is the basis of accurate quantification combined with high spatial resolution, two features that represent the main advantages of PET as compared to SPECT.

The most widely used PET tracer is 2-deoxy-2-[\(^{18}\)F]fluoro-D-glucose (FDG). FDG is a substrate analog of glucose, and in the brain it competes with glucose for the carrier-mediated transport sites in the blood brain barrier. After entering the cerebral tissue, both FDG and glucose undergo phosphorylation by hexokinase. Following phosphorylation, glucose-6-PO\(_4\) either proceeds down the glycolytic pathway or is converted to glycogen. FDG-6-PO\(_4\), on the other hand, is not a significant substrate for either of these pathways, and it does not diffuse through membranes, but it is trapped and accumulates in cells in proportion to local cerebral metabolic rate for glucose metabolism.

Utilization of FDG PET in clinical epilepsy emerged from initial observations showing localized glucose metabolic changes (interictal hypo- and ictal hypermetabolism) in patients with partial epilepsy (30-32). Following this, numerous studies using FDG as a PET tracer demonstrated a high incidence of localized interictal glucose hypometabolism in partial epilepsies (33-37), and the method became a useful clinical diagnostic tool in selected patients with intractable epilepsy who undergo presurgical evaluation.

1.3.1. Interictal FDG PET in epilepsy. Interictal FDG PET has proven to be a reliable clinical test for identifying dysfunctional cortical regions of hypometabolism that correspond, in general, to the location of epileptic foci. Comparative studies of interictal FDG PET and MRI indicated that regional cerebral glucose hypometabolism occurs more frequently than does focal cerebral structural abnormality in groups of patients with partial epilepsy (38-46). It is now well established that FDG PET is able to correctly lateralize and localize the temporal epileptic focus in a vast majority of cases, and its sensitivity surpasses that of MRI including hippocampal volumetry and proton MRS in EEG-defined unilateral temporal lobe epilepsy (46,47). In patients with lateralized but non-localizing surface EEG, FDG PET correctly localized the epileptic
temporal lobe in 79%, and, perhaps more strikingly, PET findings were consistent with unilateral temporal seizure onset as defined by invasive EEG in 45% of cases even with non-lateralizing surface EEG (48). These results suggested that FDG PET may have better correlation with intracranial than with surface EEG findings in such patients; thus, it can reduce the number of patients with temporal lobe epilepsy who require intracranial EEG studies.

Another powerful application of FDG PET has been demonstrated in children with West-syndrome, a unique age-specific and frequently malignant epileptic syndrome, characterized by infantile spasms, hypsarrhythmic EEG, and mental retardation. Infantile spasms are traditionally classified as generalized seizures (49). Initial FDG PET studies on infants with infantile spasms, however, revealed a significant proportion of patients with focal cortical abnormalities (26). Subsequent studies on large cohorts of patients confirmed that about 20% of infants with cryptogenic infantile spasms have a single cortical focus of abnormal glucose metabolism on PET scans (50), and these often correspond to focal features on the EEG (51). These PET findings and the success of cortical resection strongly suggested the key role of abnormal cerebral cortex in the initiation of seizures in children with infantile spasms (52).

1.3.2. Limitations of FDG PET in focus localization. Despite the high yield of FDG PET in localizing temporal lobe epileptic foci, initial studies in patients with neocortical, especially frontal lobe epilepsy reported a lower sensitivity, with the observation of cortical glucose hypometabolism in about 60% of cases (53, 54). Using quantitative FDG PET data analysis, Swartz et al. (45) later reported a sensitivity of 96% (81% in non-lesional cases) and a specificity of 74-78% of FDG PET for seizure focus detection in adult patients with frontal lobe epilepsy. More recently, using a high resolution PET scanner, a lobar sensitivity of 92% in the detection of frontal lobe epileptic foci with FDG PET in children was reported by our group, with a specificity of 62.5% (55). However, the consistent observation of large areas of glucose hypometabolism on PET extending beyond the epileptogenic region has precluded the use of FDG PET to define precisely the boundary of the epileptogenic zone for surgical resection (33, 55, 56). It should be emphasized that the above cited studies applied qualitative or, at best, semiquantitative methods of PET focus localization, with the lack of ability to precisely compare location and spatial extent of EEG-defined epileptic foci with objectively identified PET abnormalities.
A further limitation of FDG PET in epilepsy is that decreased glucose metabolism is not at all specific for epileptic brain regions. Hypometabolism occurs in conjunction with significant neuronal loss (irrespective of epileptogenicity), and this generally precludes successful application of FDG PET for localization of seizure foci in epilepsies associated with structural brain lesions (other than hippocampal atrophy). Moreover, it has been increasingly recognized that glucose hypometabolism of cortical and subcortical areas can often be linked to a variety of neuropsychological abnormalities associated with epilepsy, although these regions often seem not to be related to epileptogenicity. In fact, FDG PET provides an unparalleled clinical tool to assess extent and degree of hemispheric dysfunction in patients with epilepsy, as it allows assessment of functional integrity of non-epileptogenic regions. This is especially relevant in pediatric epilepsy surgery decision-making (57, 58), but it can be extremely difficult to decipher FDG PET abnormalities related to non-epileptic brain dysfunction from those specifically related to seizure foci.

1.3.3. Novel PET tracers may be more specific for epileptogenic regions. In parallel with FDG PET studies performed in multiple epilepsy centers worldwide, an increasing number of other PET tracers has been introduced to visualize and measure various functional modalities of the brain, e.g. regional cerebral blood flow, oxygen extraction, central benzodiazepine receptor binding, opiate receptor binding, histamine receptor binding, and serotonin synthesis. In fact, most of the ongoing efforts in PET research in the field of epilepsy aimed at developing novel tracers targeting various neurotransmitter systems, since such tracers are believed to be highly sensitive and show increasing specificity for epileptogenic cortex.

Among several proposed PET tracers targeting different brain neurotransmitter systems (e.g. $^{11}$C]carfentanil for mu-opiate receptors [59], $^{11}$C]doxepin for histamine H1 receptors [60], (S)-[N-methyl-$^{11}$C]ketamine for NMDA-receptors [61], or $^{11}$C]methyl-L-tryptophan for measuring brain serotonin synthesis [62, 63]), $^{11}$C]flumazenil (FMZ) emerged as one of the most promising ones (64, 65). FMZ is a ligand which binds to GABA$_A$ receptor complex, the major binding site of GABA. GABA is the major inhibitory neurotransmitter in the human brain and it plays a key role in regulating central nervous system excitability and susceptibility to seizures (66-68). Involvement of GABAergic mechanisms in the pathophysiology of human epilepsy is now widely accepted.
Initial studies of FMZ PET in temporal lobe epilepsy surgery patients found it to be more sensitive and accurate in delineating the seizure focus than FDG PET (37, 65). Subsequently, a comparison of FDG and FMZ PET in patients with frontal lobe epilepsy reported a good correlation between location of FMZ PET abnormalities and epileptic focus identified by surface and, occasionally, by intracranial EEG (69). Furthermore, FMZ PET abnormalities were generally less extensive than corresponding abnormalities shown by FDG PET. Nevertheless, although FMZ PET became available in a number of epilepsy surgery centers worldwide, the electrophysiological and clinical significance of FMZ (similarly to FDG) PET abnormalities remained poorly understood. In fact, by the end of the 1990’s, the number of studies rigorously comparing ictal scalp and intracranial EEG data with FDG and especially FMZ PET findings (reviewed by the author in [70]) remained surprisingly low.

1.3.4. Can application of PET improve outcome of resective epilepsy surgery? Although FDG PET is widely used to assist localization of potentially epileptic brain regions, and recently emerging PET tracers are being increasingly applied and evaluated in several centers, a little is known regarding the effect of resection of brain regions abnormal on PET to the outcome of neocortical epilepsy surgery. In fact, although the ultimate proof of successful preoperative delineation of the epileptogenic cortex is the prolonged alleviation of seizures after surgical resection, no quantitative studies have been performed to evaluate whether completeness of resection of cortex with preoperative PET abnormalities is related to a favorable outcome of neocortical epilepsy surgery. Such studies would be, however, substantial for determining the clinical utility of new PET tracers in assisting tailored cortical resections in patients with intractable epilepsy.
2. OBJECTIVES

1. To determine ictal intracranial electrophysiological correlates of objectively identified FDG and FMZ PET abnormalities in patients with extratemporal and non-lesional epilepsy of neocortical origin. In order to achieve this goal, we have applied objective identification and marking of PET abnormalities followed by MRI/PET/EEG co-registration and three-dimensional (3D) brain surface rendering to directly correlate PET abnormalities with intracranial EEG findings.

2. To determine electro-clinical correlates of FDG and FMZ PET abnormalities in patients with intractable neocortical epilepsy associated with MRI-verified brain lesion, and to assess the value of FMZ PET in detection of dual pathology.

3. To determine whether completeness of resection of cortex with preoperative FDG and/or FMZ PET abnormalities is related to the outcome of cortical resection.
3. SUBJECTS AND METHODS

3.1. Subjects

The subjects for all presented PET studies were selected from the FDG and FMZ PET databases of the PET Center of Children’s Hospital of Michigan. This PET Center performed approximately 3250 FDG PET (1650 pediatric and 1600 adult), and more than 400 FMZ PET studies with neurological indications between January 1994 and December 2001. In general, all patients included in the presented studies underwent presurgical evaluation due to medically intractable epilepsy. These evaluations always included video-EEG monitoring using scalp/sphenoidal electrodes, multisequence MRI (including high resolution volumetric studies) and FDG PET as well as neuropsychological evaluation. Further studies, such as intracranial EEG monitoring, intraoperative electrocorticography, and FMZ PET have been also performed, where indicated. Further characteristics of the studied patient groups are specified in the Result section for each particular study.

3.2. Methods

3.2.1. PET scanning protocol. PET studies were performed using the CTI/Siemens EXACT/HR whole body positron tomograph located at Children’s Hospital of Michigan, Detroit. This scanner has a 15 cm field of view and generates 47 image planes with a slice thickness of 3.125 mm. The reconstructed image in-plane resolution obtained is 6.5 ± 0.35 mm at full-width-at-half-maximum (FWHM) and 7.0 ± 0.53 mm in the axial direction for the FMZ PET and 5.5 ± 0.35 mm at FWHM and 6.0 ± 0.49 mm in the axial direction for the FDG PET.

Patients were fasted for 4 hours prior to the PET studies. Surface EEG electrodes were placed according to the International 10-20 system, and EEG was monitored throughout all PET examinations. A venous line was established for injection of FDG (0.143 mCi/kg) or FMZ (0.4 mCi/kg as a slow bolus over two min using a Harvard pump) produced using a Siemens RDS-11 cyclotron (Knoxville, TN). External stimuli were minimized by dimming the lights and discouraging interaction so that studies reflected the resting awake state. All patients had their PET performed in interictal state. For the FMZ PET, a 60 min dynamic PET scan of the brain.
was performed (sequence: 4x30s, 3x60s, 2x150s, 2x300s, 4x600s), beginning at the time of injection. Summed images representing activity concentration between 10-20 minutes were used to display GABA\textsubscript{A} receptor binding in brain. This procedure is especially advantageous in young patients because it does not require collection of arterial blood samples. It has been shown previously by our group that abnormalities defined in FMZ activity images based on this time frame and using a threshold of 10% for defining areas with abnormal asymmetry (see below) are essentially equivalent to those obtained from corresponding parametric volume of distribution images (71). For the FDG PET, a 20 min static emission scan was initiated 40 min after tracer injection.

3.2.2. MRI studies. MRI studies were performed on a GE 1.5 Tesla Signa 5.4 unit (GE Medical Systems, Milwaukee, Wisconsin) located in the Children’s Hospital of Michigan. For PET co-registration and partial volume correction, volumetric imaging was performed utilizing a spoiled gradient echo (SPGR) sequence. The 3D SPGR sequence generates 124 contiguous 1.5 mm coronal sections of the entire head using a field of view of 240 mm. In studies on patients with brain lesion, axial and coronal fluid-attenuated inversion recovery (FLAIR) images were also used where the lesion could not be adequately visualized and delineated on the volumetric images.

3.2.3. MRI/PET coregistration. Matching of PET and MRI image volumes was performed using a multi-purpose three-dimensional registration technique (MPItool) developed by the Max-Planck-Institute in Cologne, Germany (72). This co-registration method is highly interactive and is based on the simultaneous alignment of PET/MRI contours, which are exchanged in three orthogonal cuts through the brain. The advantage of the procedure is that it does not require external landmarks and can be used despite alterations in normal brain anatomy. Validation studies (72) showed a high reproducibility with an average displacement between PET and MRI images of less than 0.5 mm, which was always smaller than the PET image resolution. The coregistered PET and MRI image volumes were transferred to an SGI OCTANE workstation and partial volume correction of the PET images was performed, where indicated, using an established method (73).
3.2.4. Partial volume correction of PET images. Partial volume effects occur at the boundary of brain structures with different tracer activity (such as gray/white matter, gray matter/CSF border or structural lesion/normal cortex border) due to limited spatial resolution of PET images. These effects can be especially relevant if the analyzed structures are smaller than twice the FWHM of the imager resolution (74). In such cases, failure to correct for partial volume averaging leads to an underestimation (or overestimation) of the severity of functional abnormalities. Therefore, we applied correction for partial volume effects when measuring activity in small brain volumes (such as hippocampus), and in lesional/perilesional cortical regions.

In brief, following removal of the skull, MRI images were segmented into gray matter, white matter and cerebrospinal fluid (CSF) yielding three binary masks. These masks had a value of 1 if the voxel belonged to a particular class and 0 otherwise, yielding the gray matter mask \(X_G\), white matter mask \(X_W\) and CSF mask \(X_C\). Furthermore, the average value for white matter in the PET image was obtained from the centrum semiovale \(I_W\) and the average value for the CSF in the PET image was obtained from the ventricles \(I_C\). The partial volume correction for gray matter in the PET image \(I_G(r)\) was then given by

\[ I_G(r) = \frac{I_{\text{obs}}(r) - I_W(X_W \ast h) - I_C(X_C \ast h)}{X_G \ast h} \]  \hspace{1cm} (1)

where \(I_{\text{obs}}(r)\) is the original PET image volume, \(r\) is the voxel position, \(h\) is the three-dimensional point-spread function of the PET scanner and \(\ast\) denotes the convolution operation. Only voxels within the gray matter were corrected.

3.2.5. PET image analysis.

3.2.5.1. Visual assessment. Before image processing and quantitative analysis, all PET images underwent a visual assessment. Since our objective method of PET image analysis precluded detection of symmetrical bilateral PET abnormalities of homologous cortical regions, a visual evaluation was used to ensure that no focal areas of abnormal glucose metabolism or FMZ
binding (including decreases or increases) were seen in the hemisphere contralateral to the EEG-defined epileptic focus. The evaluator was unaware of other localizing information (except the EEG obtained during PET scanning) at the time of the evaluation. In general, visual assessment was used only to exclude PET images from further quantitative processing, but findings of visual evaluation were not used for our presented studies.

3.2.5.2. Analysis of cortical PET abnormalities

3.2.5.2.1. Definition and 3D surface rendering of cortical PET abnormalities. In studies of patients with epilepsy of neocortical origin, the extent of regional cortical abnormalities of brain glucose metabolism and FMZ binding was identified using an objective method based on a semi-automated software package applied to all supratentorial axial planes of the PET image volume (75). This procedure allows the definition of abnormal cortical areas of glucose metabolism or FMZ binding based on an asymmetry index (AI) derived from contralateral homotopic cortical areas according to a predefined cutoff threshold, determined using PET images of healthy normal controls (75, 76). The AI is defined as:

\[
\text{AI(\%)} = \frac{[(H-L)/(H+L)/2]}{x100}\% \tag{2}
\]

where H indicates the higher profile element and L indicates the lower profile element. Those cortical areas which exceeded a given asymmetry threshold (normal mean asymmetry + 2 SD) were marked on the side of the epileptic focus (Figure 1). A "marked file" containing the cortical regions with abnormal asymmetry was created for each PET study. The smallest possible abnormality defined in the PET images using this method to detect cortical asymmetries consisted of at least three adjacent segments in two consecutive planes yielding an area of about 1 cm².

**Figure 1** Objective definition of cortical PET abnormalities. Activity profile obtained from an axial FDG PET plane. Activity in the hemisphere ipsilateral to the epileptic focus is indicated by red and in the contralateral cortex by yellow line. Cortical sectors with abnormal (>10%) asymmetry are shown as red areas, the height of which is proportional with the degree of asymmetry. The profile demonstrates that, in this case, maximum hypometabolism occurred in the posterior parietal region whereas cortex giving rise to seizures (seizure onset) showed only subtle (<10%) glucose hypometabolism.
The coregistered volumetric MRI and the marked PET files were further processed using the 3D-Tool software package (77) that combines methods for segmentation, visualization, and quantitative analysis of coregistered multimodality volume data. In brief, the brain was automatically segmented from MRI data using morphological operations, and 3D surface views were created. Functional data obtained the marked PET image volumes were projected onto the brain surface (Figure 2) (78), and correlated with intracranial EEG data (see in 3.2.5.2.3.).

Figure 2. Cortical areas of decreased glucose metabolism displayed on the 3D-reconstructed brain surface. Areas with >10% decrease of glucose metabolism in the left hemisphere (as compared to the contralateral homologous regions) are marked and displayed in red on the surface reconstructed from volumetric MRI.

3.2.5.2.2. Spatial comparison of cortical structural vs. functional (PET) abnormalities. In studies of patients with epilepsy and cortical lesions, the location and extent of the lesion was
also displayed on the 3D reconstructed brain surface, thus allowing a direct comparison between the size and location of structural vs. functional abnormalities. The lesions were defined by projecting their greatest cortical extension onto the cortical surface, thus displaying the full size of the lesion as an area on the brain surface. The procedure is described in detail in Juhász et al. (76). Using this method, the surface extent of the structural lesion as well as that of the marked PET abnormalities could be obtained and expressed in cm². A similar procedure was employed for postoperative MRI images, where the location and extent of cortical resections were displayed on the 3D cortical surface reconstructed from the coregistered preoperative MRI image volume (79).

3.2.5.2.3. Spatial comparison of intracranial EEG findings with the surface rendered PET abnormalities. The exact surface location of subdural electrodes was determined and visualized on the 3D reconstructed brain surface by utilizing digitalized radiographic (X-ray) images acquired with the subdural electrode arrays in place (80, 81). The main advantage of this method is that skull X-rays (unlike MRIs) can easily be obtained at the bedside, thus, this procedure does not require disconnection of EEG electrodes or transportation. This method is also cheap and especially preferable in children where sedation is often required during MRI procedures. In brief, three metallic fiducial markers were placed at standard locations on the patients’ head and a planar X-ray image was acquired. The X-ray was then digitized and the fiducial markers were identified on it as well as on the corresponding 3D reconstructed MRI image volume, using the 3D-Tool software package. An iterative algorithm minimized the differences between the two sets of coordinate triplets by adjusting the three euler-angles and the image zoom (82). As a result, a cortical surface view was created allowing the location of electrodes to be directly defined on the MRI 3D brain surface (Figures 2 and 3).
3.2.5.3. Analysis of FMZ PET abnormalities in patients with dual pathology using regions of interest (ROIs). In studies of FMZ PET abnormalities of patients with dual pathology, an MRI-based ROI analysis was applied to measure FMZ binding in the whole hippocampus and three hippocampal subregions (anterior, middle and posterior hippocampus) (83). Unilateral hippocampal atrophy was identified by MRI-based hippocampal volumetry. The ROIs were manually defined on each coronal SPGR MRI image plane where the given structure could be clearly visualized, using a previously defined protocol. All ROIs defined on MRI images were copied to the co-registered, partial-volume corrected FMZ PET images, and a weighted average concentration for each structure was obtained. Asymmetries of FMZ binding were then calculated using an asymmetry index (AI; see above). Normal asymmetries of FMZ binding were defined by FMZ PET measurements of 6 normal healthy subjects. Cortical sites of decreased FMZ binding were defined by FMZ PET measurements of 6 normal healthy subjects. Cortical sites of decreased FMZ binding were also evaluated using AIs for regions with MRI-verified cortical lesions and for non-lesional areas with visually detected asymmetry.

3.2.6. EEG procedures. All patients underwent prolonged video-EEG recordings with scalp/sphenoidal electrodes. Furthermore, patients with neocortical epilepsy underwent
intracranial EEG monitoring with subdural electrodes or intraoperative electrocorticography (ECoG), where indicated. Subdural electrode placement was guided generally by the seizure semiology, the seizure onset area as determined by scalp ictal EEG and by the location of PET abnormalities. During chronic intracranial EEG monitoring, at least three habitual seizures were captured and analyzed, and electrodes involved in seizure onset, rapid seizure spread and frequent interictal spiking were recorded (76, 80). In studies where findings of intraoperative EcoG were used, at least 10 minutes of ECoG recording was performed and evaluated. The spiking area was defined as neocortex showing at least 10 spikes/min during the ECoG (84).
4. RESULTS

4.1. Ictal intracranial EEG correlates of cortical FDG and FMZ PET abnormalities in patients with neocortical epilepsy

4.1.1. FMZ PET is more sensitive than FDG PET in detection of seizure onset defined by intracranial EEG monitoring (70, 80). Ten patients with extratemporal foci (mean age: 11 years, age range 2 - 19 years; seizure focus: 6 frontal, 3 fronto-parietal 1 temporo-parietal) underwent both FDG and FMZ PET, and performance of these two PET modalities was compared to ictal intracranial EEG data. Using objectively marked PET images co-registered and surface rendered with high-resolution MRI scans, we found that FMZ PET detected at least part of the seizure onset in all cases, whereas FDG PET missed the area of seizure onset in two children. A receiver operating characteristics (ROC) analysis showed that the area under the ROC curves was higher for FMZ than FDG PET for both seizure onset (p=0.01) and frequent interictal spiking (p=0.04). Sensitivity of FMZ PET for detecting areas of seizure onset at the 10% asymmetry threshold was 81% ± 9%, which was associated with a 74 ± 7% specificity. In contrast, we found a low sensitivity for both FMZ and FDG PET for detecting cortical areas of rapid seizure spread. We have also analyzed PET abnormalities marked remote from the area of seizure onset (i.e. non-continuous abnormality outside the lobe of seizure onset) in 7 patients with frontal seizure onset. In these, a non-continuous parietal area of decreased FMZ binding was seen in 4 patients, while a temporal FMZ PET abnormality, mostly involving the middle temporal region, was detected in 6 (both remote areas appeared in three). Of these 10 remote areas with decreased FMZ binding, 7 were partially or fully covered by subdural electrodes, and were involved in rapid seizure spread in 6 cases. The location of remote FMZ PET abnormalities suggested that these areas may represent cortical regions synaptically connected with the primary seizure onset region and targeted by rapid cortico-cortical spread of the seizures.

4.1.2. Seizure onset occurs most often at the border of cortex with glucose hypometabolism. Since electrodes with seizure onset were often missed by FDG PET, but these electrodes were frequently found to be located in adjacent cortical regions, we performed a study on 12 young patients (mean age 10.8 years; age range 2-19 years) with neocortical epilepsy (seizure focus: 5
frontal, 3 fronto-parietal, 3 temporal and 1 temporo-parietal) and normal MRI, where subdural electrodes were classified according to their location over cortical areas which were defined as hypometabolic, normometabolic or at the border between hypometabolic and normal cortex (metabolic “borderzones”) based on FDG PET (85). Ictal onset occurred in electrodes overlying metabolic borderzones significantly more frequently than in electrodes over hypo- or normometabolic regions (26% vs. 8.9% and 4.6%; p=0.003 and p=0.0002, respectively [ANOVA]) (Figure 4).

Early seizure spread also occurred in electrodes overlying metabolic borderzones more often than in electrodes overlying hypometabolic regions (26.2% vs. 7.1%; p=0.013 [ANOVA]). Seizure spread occurred significantly more frequently than seizure onset over normometabolic areas (1.5 vs. 4.6%, p=0.0078).

Figure 4. Seizure onset at the border of hypometabolic cortex. Surface location of marked FDG PET abnormalities (hypometabolic cortex is indicated in red) versus subdural grid electrodes in a 4-year old boy with a history of infantile spasms. The figure demonstrates that ictal onset (electrodes in white) occurred over the posterior border of an extensively hypometabolic area in the left temporo-occipital region. Note that several electrodes overlying the left temporal hypometabolism were not involved in seizure onset.
4.2. Electroclinical correlates of FDG and FMZ PET in patients with intractable epilepsy and MRI-verified brain lesion

4.2.1. FMZ PET is more accurate than FDG PET in detection of perilesional epileptic cortex. Our study of patients with brain lesion included 17 subjects (10 adults and seven children, mean age 21.7 years, age range 5-42 years), who underwent presurgical evaluation including FDG and FMZ PET studies (76). The mean surface extent of FMZ PET abnormalities (after partial volume correction) was significantly larger than the corresponding structural lesions (p=0.015; paired t-test), but it was significantly smaller than corresponding areas of glucose hypometabolism measured using FDG PET (p=0.005). The size of FDG abnormalities was in average 1.9 (range 1.03 - 9.4) larger than that of the corresponding FMZ abnormalities. The size of perilesional FDG PET abnormalities (expressed as a PET/lesion size ratio) showed a significant correlation with the estimated life-time number of seizures (Kendall’s tau=0.47, p=0.019) as well as with the estimated life-time number of partial seizures (Kendall’s tau=0.45, p=0.025). The extent of perilesional FMZ PET abnormalities did not show any correlation with the seizure number, but showed an excellent correspondence with spiking cortex, the resection of which resulted in seizure-free outcome in all but one operated patients. FMZ PET abnormalities detected 80% of spiking cortex while decreased FMZ binding occurred only over 11% of non-spiking areas covered by electrodes (sensitivity: 80%, specificity: 89%). Remote FMZ PET abnormalities (found in 6 patients) were significantly associated with early age of seizure onset (3.5 ± 4.1 years vs. 15.1 ± 12.7 years, p=0.048; unpaired t-test), and a similar tendency was found for long duration of epilepsy (patients with remote FMZ PET abnormalities had in average 7.5 longer duration of epilepsy; p=0.09). No similar differences could be found for the presence vs. absence of remote FDG PET abnormalities.

4.2.2. FMZ PET is highly sensitive for detection of dual pathology. Twelve patients (mean age 25.4 years, age range 15 - 41 years) with localization related epilepsy and MRI-verified dual pathology were included in this study (83). FMZ binding of the whole volume of the hippocampus was abnormal in nine patients, whereas subregional analysis showed abnormal values in at least one portion of the atrophic hippocampi in all cases (Figure 5).
Cortical regions of decreased FMZ binding were detected by visual evaluation in every patient. The localization of these regions corresponded well to MRI-defined structural lesions. AIs for these cortical regions with MRI abnormality were between 12.3 and 123 (mean: 49.2 ± 39.6). The highest AI values were found over ROIs with infarcts (n=4), cysts (n=2) and ganglioglioma (n=1), all of them showing AIs above 40. In four cases, FMZ PET showed decreased binding on visual evaluation in additional cortical areas, where MRI did not reveal structural abnormality. AIs for these cortical regions were between 8.9 and 19.0 (mean: 12.8 ± 3.8), and these were significantly lower than those for lesional ROIs measured in the same patients.

4.3. Relationship of PET abnormalities to the outcome of neocortical epilepsy surgery

We analyzed the data of 15 young patients (mean age 12.2 ± 7.0 years, age range 1.5 - 21 years) with intractable epilepsy of neocortical origin (79). The patients underwent cortical resection following preoperative MRI (normal in nine and showing structural lesions in the remaining six), surface (n=15) and subdural (n=11) EEG monitoring as well as FDG and FMZ PET examinations. Postoperative follow-up time was at least 12 months (mean: 21.5 ± 9.5 months, median: 17 months, range: 12-41 months). Postoperative outcome (class I-V) was determined according to the criteria of Engel. After surgery, 8 patients (53 %) became seizure-free (class I outcome), 1 had class II outcome, 4 showed a worthwhile improvement (class III) and 2 had class IV outcome (no worthwhile improvement). Preoperative size of total FMZ PET abnormalities showed a significant correlation with the outcome (r=0.57, p=0.025; Spearman’s rank correlation). No similar correlation was found between outcome and the total size of FDG
PET abnormalities ($r=0.29$, $p=0.30$). The correlation between outcome and the size of presurgical perifocal PET abnormalities was marginal for FMZ ($r=0.5$, $p=0.056$) and non-significant for FDG PET ($r=0.28$, $p=0.3$). The total size of preoperative FDG (14.3 ± 12.6% vs. 18.6 ± 17.7%; $p=0.60$) or FMZ PET (6.3%±6.4% vs. 14.3 ± 4.8%; $p=0.19$) abnormalities was not different in patients who became seizure-free ($n=8$) as compared to those who continued to have seizures ($n=7$).

The size of non-resected cortex with perifocal FMZ PET abnormalities showed a positive correlation with the outcome scores ($r=0.66$, $p=0.007$), i.e., larger residual cortex with FMZ PET abnormalities in the lobe of seizure onset was associated with a worse outcome (Figures 6 and 7).

**Figure 6** Non-resected cortex with PET abnormalities vs. surgical outcome. Non-resected cortex with preoperative PET abnormalities in the lobe of seizure onset showed significant correlation with the outcome for FMZ PET (black circles; $p=0.007$), but not for FDG PET (open circles; $p=0.24$). Patients with class II and III outcome were pooled in one group on the figure because only one patient had class II outcome (percent non-resected cortex abnormal on FMZ PET was 0 in this patient).

**Figure 7**. Surface distribution of marked FDG (red) and FMZ (white) PET abnormalities as well as the region of cortical resection (black) in a patient with left posterior parietal seizure focus. The figure shows that the bulk of the cortex with decreased FMZ binding was removed, while the majority of the hypometabolic cortex was not resected. The patient has been seizure-free for 40 months.
No similar correlations were found for non-resected cortex with perifocal FDG PET abnormalities (p=0.61). The correlation between non-resected perifocal FMZ PET abnormalities and the outcome scores persisted in patients with extratemporal resection (r=0.73, p=0.007) and also in patients with no lesion on MRI (n=10; r=0.60, p=0.049). In a logistic regression analysis, the percent size of non-resected perifocal cortex with FMZ PET abnormalities had a marginally significant (p=0.055) effect on seizure-free outcome, whereas neither the localizing value of MRI and/or surface EEG findings (p=0.71) nor the non-resected remote FMZ PET abnormalities (p=0.66) had a significant effect on seizure-free outcome. Finally, the effect of non-resected FDG PET abnormalities on seizure-free outcome was non-significant (p=0.50 for perifocal, and p=0.27 for remote FDG PET abnormalities).
5. CONCLUSIONS

1. Objectively marked, 3D surface rendered PET abnormalities enable direct comparison of functional abnormalities detected by PET with those provided by intracranial EEG monitoring. 3D multimodality imaging facilitates accurate comparison of structural and functional abnormalities in epileptic brain regions. Objectively identified cortical FMZ PET abnormalities proved to be significantly more sensitive than FDG PET abnormalities for detection of cortical regions of seizure onset and frequent interictal spiking in patients with extratemporal epilepsy, as defined by intracranial EEG monitoring. The intimate association between cortex with decreased FMZ binding and the zone of seizure onset has been subsequently demonstrated by another group (87). Thus, application of FMZ PET during presurgical evaluation can enhance coverage of the epileptogenic zone by intracranial electrodes. Decreased FMZ binding remote from the area of seizure onset may represent, in some cases, functional involvement of directly connected regions, which may be targeted by rapid seizure involvement. In other cases such areas may indicate dysplastic but not epileptogenic cortex. Dysplastic cortex can show not only decreased but, occasionally, also increased FMZ binding (88), although electrophysiological significance of such areas remains to be elucidated. Further studies are warranted to determine under which circumstances should be remote areas also resected to achieve long-term seizure control.

In patients with non-lesional neocortical epilepsy, seizure foci are often located at the border of cortical areas with decreased glucose metabolism seen on FDG PET, rather than within or in the center of hypometabolic areas. This finding is at odds with the generally accepted concept that focal areas of hypometabolism represent epileptic cortex. In fact, our study demonstrates that ictal electrophysiological changes often skip or “flow” around truly hypometabolic areas, which appear to be often protected against seizure involvement. Thus, cortical areas with hypometabolism should be interpreted as regions most likely not involved in seizure activity, while surrounding cortex should be carefully addressed in presurgical evaluation, if FDG PET is used to guide subdural electrode coverage. The pathophysiological basis of this phenomenon is not clear. Possible explanations of our findings emerge from animal studies of experimental epilepsy. It has been demonstrated that cortical epileptic foci and surrounding cortical zones display different, occasionally even opposite
electrophysiological, metabolic and neurochemical properties (89-95). Actively spiking epileptic foci show increased glucose metabolism (96) and were shown to be surrounded by widespread hypometabolic cortex, which extended in a dynamic fashion during transition from interictal to ictal activity (93). It was also demonstrated that electrophysiologically hyperexcitable cortical regions may show normal glucose metabolism in experimentally induced cortical dysplasias (97). Acutely induced focal seizure activity, however, is usually associated with increased metabolism in the focus and decreased metabolism in ipsilateral connected areas (98). In this model, [14C]2-deoxyglucose uptake was related to the overall strength of synaptic activity, and reduced metabolism was found to be associated with decreased synaptic activity and tonic hyperpolarization of the neurons. Such electrophysiological characteristics may protect these cortical areas from ictal involvement, and can represent a functional disconnection of the focus from surrounding synaptically connected areas. The functional isolation of epileptic foci from their surrounding neuronal connections may influence the excitability of this neuronal population and may prevent self-sustaining synchronized neuronal activity as well (99), as shown by successful suppression of focal epileptic activity by subpial transections both in animal models and in human epilepsy surgery of eloquent cortex (100-102). Based on these observations one can hypothesize that hypometabolic cortex without ictal electrophysiological involvement represents regions with functional abnormality, that are actually protected against participation in the seizure activity. This hypothesis is also supported by recent findings showing a down-regulation of brain-derived neurotrophic factor and other molecules in areas surrounding the epileptic focus, which likely represents an inhibitory surround that hampers seizure spread (94, 95). This is consistent with our findings that while both onset and spread were equally rare over hypometabolic areas, the involvement of normometabolic areas was higher during seizure spread, suggesting that early spread occurs preferentially in normo- rather than hypometabolic regions.

2. In patients with epilepsy and cortical lesion, FMZ PET is able to delineate perilesional epileptic cortex as defined by intracranial EEG, and it may be especially useful to localize such areas in patients with extensive perilesional glucose hypometabolism. These findings are consistent with previous electrophysiological studies demonstrating that epileptogenic brain tissue is commonly located in an eccentric position rather than completely surrounding the lesion (10, 103). Similar pattern for perilesional areas of abnormal GABA_A receptor binding may be
especially important when the lesion is close to an eloquent cortical region thus limiting the possible boundaries of the surgical resection.

Correlation of extensive perilesional hypometabolism with the life-time number of seizures may reflect progressive cortical dysfunction due to chronic epilepsy. The progressive nature of hypometabolism has been shown previously in patients with temporal lobe epilepsy (104), but the chronic, seizure-related spatial extension of such abnormalities is a novel finding. Perilesional FMZ PET abnormalities seem to remain spatially restricted even in patients with large life-time number of seizures, while remote cortical areas seem to undergo FMZ binding changes after a sufficiently long duration of epilepsy, especially in patients with early onset of epilepsy.

FMZ PET is very sensitive for detection of dual pathology. Volumetric MRI-defined hippocampal atrophy, even if it is mild, is always associated with decreased FMZ binding, although the latter may be localized to only one subregion of the hippocampus. Thus, FMZ PET can be useful in selected patients with a potentially epileptogenic brain lesion when presence of dual pathology is suspected or to be excluded, e.g., from discordant EEG, clinical, and structural imaging data. Quantitative analysis of hippocampal subregions is occasionally required to detect focal decrease of GABA_A-receptor binding in the hippocampus. Presurgical identification of dual pathology is of major practical importance since it has been demonstrated that resection of both the epileptogenic cortical lesion and the atrophic hippocampus is required to obtain optimal surgical results in patients with dual pathology (105, 106).

3. Our findings demonstrate that patients with extensive cortical FMZ PET abnormalities are likely to continue to have seizures postoperatively. On the other hand, seizure-freedom can be achieved if the cortex with decreased FMZ binding is completely removed. Further, resection of cortical areas with decreased FMZ binding can lead to long-term alleviation of seizures even in the presence of large non-resected regions of glucose hypometabolism. Thus, FMZ PET can assist surgical planning in patients with extensive unilateral cortical hypometabolism. Remote FMZ PET abnormalities (outside the lobe of seizure onset) in the resected brain did not show significant correlation with the outcome, and the contribution of such areas to surgical prognosis
remains uncertain. Non-resected remote FMZ PET abnormalities, as shown in the present study, were associated with seizure-free outcome in several cases suggesting that these regions are not always epileptogenic. In such cases, these areas might represent abnormal (e.g. dysplastic) but not epileptogenic cortex, or cortical regions receiving seizure spread but which are not able to generate independent epileptiform activity or give rise to seizures. This is supported by the fact that remote FMZ PET abnormalities may occur in projection areas (76, 107), and may normalize after successful surgery as suggested by a follow-up study of a small series of patients (107). In contrast, although FDG PET abnormalities correctly regionalize the epileptogenic area in most cases, their size is not related to the extent of epileptogenic tissue to be removed. This, again, suggests that decreased cortical glucose metabolism is not directly related to epileptogenicity, and reinforces that more specific tracers are required and can be successfully used to identify epileptogenic brain regions in selected patients with intractable epilepsy of neocortical origin.
Acknowledgements: I am grateful to prof. Imre Szirmai from whom I learned that high quality clinical research requires meticulous collection and systematic analysis of the data, and that these can easily become garbage without correct interpretation and logical presentation of the findings. I express my gratitude to prof. Harry T. Chugani and his wife, Diane, in the PET Center of Children’s Hospital of Michigan, Detroit, who gave me the opportunity to join their lab and let me develop my independent line of research. I am thankful to a number of colleagues in Detroit without whom these studies could not have been performed: to Ferenc Nagy M.D., who helped me to make a jump-start during the most difficult first months at the PET Center in Detroit; to Otto Muzik Ph.D., physicist, who provided an excellent technical and methodological support for all my studies; to Tom Mangner Ph.D. and Pulak Chakraborty Ph.D., the chemists who developed and provided the PET tracers in a very reliable manner; to Galina Rabkin, CNMT, Teresa Jones, CNMT, Mei-li Lee, M.S., Giselle Baillargeon, RN, and Kris Baird for their expert technical assistance in performing the PET studies; to Aashit Shah M.D., Jagdish Shah M.D., Sunny Phillip M.D., and Eishi Asano M.D., who provided excellent EEG data; to prof. Craig Watson, director of the Comprehensive Epilepsy Surgery Program at Wayne State University, for his support and always valuable advice; to prof. Alexa Canady M.D., and Sandeep Sood M.D., who performed the surgical resections; to William Kupsky, M.D., who performed the histological studies on the resected specimens; and to prof. Joel Ager Ph.D., and James Janisse Ph.D., bio-statisticians for their expert statistical support. I am very thankful to the children and adults who were subjects of these studies.
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SUMMARY

The success of cortical resection for intractable epilepsy of neocortical origin is highly dependent on the accurate presurgical delineation of the regions responsible for generating seizures. In addition to EEG and structural imaging studies, functional neuroimaging such as positron emission tomography (PET) can assist lateralization and localization of epileptogenic cortical areas. In the presented studies, objectively delineated focal PET abnormalities have been analyzed in patients (mostly children) with intractable epilepsy, using two different tracers: 2-deoxy-2-[\(^{18}\)F]fluoro-D-glucose (FDG), that measures regional brain glucose metabolism, and \([^{11}\)C]flumazenil (FMZ), that binds to GABA\(_A\) receptors. The PET abnormalities were correlated with scalp and intracranial EEG findings, structural brain abnormalities, as well as surgical outcome data. In patients with extratemporal foci and no lesion on MRI, FMZ PET was more sensitive than FDG PET for identification of the seizure onset zone defined by intracranial EEG monitoring. In contrast, seizures commonly originated from the border of hypometabolic cortex detected by FDG PET suggesting that such areas are most likely epileptogenic, and should be addressed if subdural EEG is applied to delineate epileptic cortex. In patients with cortical lesions, perilesional cortex with decreased FMZ binding was significantly smaller than corresponding areas of glucose hypometabolism, and correlated well with spiking cortex. Extent of perilesional hypometabolism, on the other hand, showed a correlation with the life-time number of seizures suggesting a seizure-related progression of brain dysfunction. FMZ PET proved to be also very sensitive for detection of dual pathology (coexistence of an epileptogenic cortical lesion and hippocampal sclerosis). This has a major clinical importance since resection of both the cortical lesion and the atrophic hippocampus is required to achieve optimal surgical results. Finally, we demonstrated that in patients with neocortical epilepsy, FDG PET abnormalities correctly regionalize the epileptogenic area, but their size is not related to the extent of epileptogenic tissue to be removed. In contrast, complete resection of cortex with decreased FMZ binding predicts good surgical outcome suggesting that application of FMZ PET can improve surgical results in selected patients with intractable epilepsy of neocortical origin.

Összefoglaló

Neokortikális epilepsziák sikertelen gyógyászati kezelése esetén az epilepszias főkusz sebészti rezkciója megszüntetheti a rohamokat. A műtét utáni rohammentesség azonban jelentősen függ
az epileptogén területek preoperatív lokalizálásának pontosságától. Ebben funkcionális képkalkotó technikák, pl. pozitron emissziós tomográfia (PET) alkalmazása jelentős segítséget nyújthat, különösen ha non-invazív EEG és strukturális képkalkotó (CT, MRI) vizsgálatok nem adnak pontos információt a rezekálódó epileptogén kérgi területek helyéről és kiterjedéséről. Az értekezésben összefoglalt vizsgálatok során objektív módszerrel meghatározott fokális PET eltéréseket elemezettünk kétfélé PET tracer alkalmazása során. 2-Deoxy-2-[¹⁸F]fluoro-D-glukóz (FDG) PET az agyi glukóz metabolizmus körülfő eltéréseit mutatja ki, míg [¹¹C]flumazenil (FMZ) PET a gátoló hatású GABAₐ receptorok működészavarát képes in vivo detektálni. A PET abnormitások háromdimenziós agyfelszínre vetített helyét és kiterjedését elemezhetünk intrakraniális epileptiform EEG eltérések, MRI-vel kimutatott strukturális léziók, valamint a műtéti kimenetel függvényében. Eredményeink azt mutatták, hogy a kérgi FMZ kötődés csökkenése pontosabban jelzi a rohamkiindulás zónáját, mint az FDG PET által jelzett hipometabolizmus. Iktálás kiindulást váratlan módon a hipometabolizmust határoló agykárgi területekről észleltünk leggyakrabban. Epileptogén strukturális léziók esetén a léziót körülvevő kérgi FMZ PET eltérések jelentős kisebbek voltak mint az azokat klsérő hipometabolizmus, és kitűnő korrelációkat mutattak az epileptiform EEG aktivitás lokalizációjával. A léziót körülvevő hipometabolizmus ugyanakkor kiterjedt volt nagyszámú rohamon átesett betegeknél. FMZ PET szenzitívná bizonyult a más módszerekkel nehezen diagnosztizálható kettős patológia (epileptogén kérgi lézió és hippocampalis sclerosis együttes előfordulása) kimutatásában is. A műtéti eredményekkel történt összehasonlító vizsgálatok azt mutatták, hogy neokortikális epilepsziáknál FDG PET ugyan alkalmas az epileptogén területek regionalizálására, de a hipometabolizmus kiterjedése nem ad megfelelő támpontot a rezekálódó területek pontos nagyságára vonatkozóan. Ezzel szemben csökkent FMZ kötődést mutató kérgi areák komplett rezekciója rohammentes műtéti kimenetelt válaszítást.