



Nuclear Medicine in Pediatric Neurology and Neurosurgery: Epilepsy and Brain Tumors

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In pediatric drug-resistant epilepsy, nuclear medicine can provide important additional information in the presurgical localization of the epileptogenic focus. The main modalities used are interictal ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) and ictal regional cerebral perfusion study with single-photon emission computed tomography (SPECT). Nuclear medicine techniques have a sensitivity of approximately 85% to 90% in the localization of an epileptogenic focus in temporal lobe epilepsy; however, in this clinical setting, they are not always clinically indicated because other techniques (eg, ictal and interictal electroencephalogram, video telemetry, magnetic resonance imaging [MRI]) may be successful in the identification of the epileptogenic focus. Nuclear medicine is very useful when MRI is negative and/or when electroencephalogram and MRI are discordant. A good technique to identify the epileptogenic focus is especially needed in the setting of extratemporal lobe epilepsy; however, in this context, identification of the epileptogenic focus is more difficult for all techniques and the sensitivity of the isotope techniques is only 50% to 60%. This review article discusses the clinical value of the different techniques in the clinical context; it also gives practical suggestions on how to acquire good ictal SPECT and interictal FDG-PET scans. Nuclear medicine in pediatric brain tumors can help in differentiating tumor recurrence from post-treatment sequelae, in assessing the response to treatment, in directing biopsy, and in planning therapy. Both PET and SPECT tracers can be used. In this review, we discuss the use of the different tracers available in this still very new, but promising, application of radioisotope techniques.

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In pediatric neurology, positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are regarded as accurate and noninvasive methods to study brain activity, to elucidate the complexities of the developing brain, and to understand disease processes. Within the first years of life, the brain undergoes a process of maturation; knowledge of the different steps of maturation of the cerebral tissue is essential for a proper interpretation of imaging tests in children.

The majority of publications that discuss the use of nuclear

medicine in pediatric neurology and neurosurgery focus on epilepsy and brain tumors and this is why a discussion of these 2 applications comprises most of this review article. However, other applications will be briefly mentioned.

Nuclear Medicine in the Management of Pediatric Epilepsy

Epilepsy is one of the most common neurological conditions, affecting nearly 1% of the entire population. Almost 60% of patients respond to the first tried antiepileptic drug. Nearly 20% to 25% of patients with epilepsy do not respond to medications and are said to have intractable epilepsy.^{1,2} Intractable or refractory epilepsy can be treated with surgery; however, surgery is a viable option in only 15% to 20% of individuals. The majority of patients undergoing surgery complain of refractory partial seizures, mainly of temporal lobe origin. Surgical procedures performed include temporal and extratemporal resections, hemispherectomy, and functional or palliative procedures like corpus callosotomy and

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multiple subpial transections.^{3,4} At any center offering epilepsy surgery services, a patient's eligibility for surgery is decided after a comprehensive assessment. The information available from clinical history and examination, magnetic resonance imaging (MRI), electroencephalogram (EEG), SPECT, and possibly positron emission tomography (PET) studies, followed by an assessment by a psychologist and a psychiatrist and, if necessary, by other investigations like invasive EEG monitoring, is gathered together and evaluated.⁵ The whole aim of the presurgical assessment is the localization of the seizure focus, the identification of the risks associated with surgery, and the estimate of the functional neurological outcome following surgery. A successful surgery is therefore dependent on the correct identification of the epileptogenic focus and the complete resection of the same.

The clinical history and examination are essential to identify the character of the epilepsy, to establish the possible lobar origin of the seizures (eg, partial seizures with automatisms may suggest temporal lobe origin), and to discover any functional deficit, be it in the motor, language or visual domains.

The patient then undergoes video EEG monitoring or telemetry to identify typical events and to document concordance between the observed focus and the abnormalities possibly shown on the MRI. In children with reported multiple seizure types, it may be possible to identify a clear focal onset of all such events, and the clinical phenotype of multiple seizures may be the result of the spread of the electrical activity from one focus to different parts of the brain. Thus, multiple seizure types may in fact represent variations of a single type. With the continuing EEG and video monitoring, one also can find out whether there are frequent unreported nocturnal events or subclinical events. It is also possible to diagnose a nonepileptic attack disorder.

In children with epilepsy, the MRI protocol is designed with emphasis on the hippocampus. Specifically, tailored MRI protocols may identify subtle abnormalities in the hippocampal and extrahippocampal regions that possibly are undetected on a routine brain MRI scan. The MRI protocol for epilepsy involves thin cuts of the brain in sagittal, coronal, and axial planes.⁶ The hippocampus is best imaged with coronal images taken perpendicularly to the long axis of the hippocampus. Volumetry and relaxometry has shown greater sensitivity and specificity for mesial temporal sclerosis.⁷⁻⁹ Documentation of hippocampal atrophy in the setting of intractable seizures of temporal lobe origin is a positive predictor for a good postsurgical outcome.^{10,11} MRI can show developmental tumors and malformations in addition to mesial temporal sclerosis.

To predict possible impairment in memory ability and academic attainments after surgery and to identify the expectations of the family from the proposed surgery, a review by a psychologist and a psychiatrist is essential. For a classification of epilepsy, see Table 1.¹²

Rationale for Functional Imaging

Epilepsy is determined by the presence of abnormal neural activity and its propagation. Visualization of this activity is

Table 1 Classification of Epilepsy¹²

A) Generalized onset
1. Seizures with tonic and/or clonic manifestations
i) Tonic-clonic seizures
ii) Clonic seizures
iii) Tonic seizures
2. Absences
i) Typical absences
ii) Atypical absences
iii) Myoclonic absences
3. Myoclonic seizure types
i) Myoclonic seizures
ii) Myoclonic astatic seizures
iii) Eyelid myoclonia
4. Epileptic spasms
5. Atonic seizures
B) Focal onset (partial)
1. Local
i) Neocortical, with and without local spread
ii) Hippocampal and parahippocampal
2. With ipsilateral propagation to
i) Neocortical areas
ii) Limbic areas
3. With contralateral spread to
i) Neocortical areas
ii) Limbic areas
4. Secondarily generalized
i) Tonic-clonic seizures
ii) Absence seizures
iii) Epileptic spasms
C) Neonatal seizures
D) Status epilepticus
i) Epilepsia partialis continua
ii) Supplementary motor area status epilepticus
iii) Aura continua
iv) Dyscognitive focal (psychomotor, complex partial)
v) Tonic-clonic status epilepticus
vi) Absence status epilepticus
vii) Myoclonic status epilepticus
viii) Tonic status epilepticus
ix) Subtle status epilepticus

more relevant than the identification of a particular lesion or structural malformation. Traditional measures of investigating epilepsy, namely EEG, and functional imaging, especially SPECT, provide separate information on the temporal and spatial resolution of the epileptogenic focus. Ideally, the best information can be obtained by correlating the functional activity of the brain to the anatomy. With advent of newer technology (like Subtraction Ictal SPECT images and co-registration with MRI [SISCOM] and Statistical Parametric Mapping [SPM]) it is now possible to correlate functional imaging to structural imaging by coregistration of SPECT and PET to MRI, with a better understanding of epilepsy.

Before making a decision on the need of functional imaging in a child being investigated for possible epilepsy surgery, it is important to define the epilepsy syndrome and the type of seizures. Seizures with electrographic onset in one part of the brain and clinically limited to focal symptoms are termed as partial seizures. The seizure activity may propagate to in-

volve the entire brain with clinical manifestation of generalized seizures, usually of tonic clonic character. Generalized seizures and complex partial seizures are by definition associated with loss of consciousness and awareness, which is preserved in patients with simple partial seizures.

Patients with a seizure semeiology of generalized tonic clonic character but a focal onset on the EEG would benefit from functional imaging like SPECT or PET, which may be concordant to the EEG focus, thus suggesting a possible candidature for surgery.

Functional imaging modalities commonly used to evaluate individuals with epilepsy include regional cerebral blood flow studies with SPECT and glucose metabolism studies with PET.¹³⁻¹⁶ The rationale for these investigations is based on the observation that, during the interictal period, the regional cerebral blood flow to the seizure focus may be reduced and the same region shows glucose hypometabolism. The reason for the reduced cerebral blood flow and glucose metabolism is still under investigation. Also, the reduction in regional cerebral blood flow is not necessarily always in parallel to the extent of hypometabolism. In the interictal phase, there seems to be an uncoupling between perfusion and metabolism,^{17,18} with a greater reduction in cerebral glucose metabolism in comparison with the reduction of cerebral blood flow; this translates into a higher positive predictive value of the interictal ¹⁸F-fluorodeoxyglucose (FDG)-PET over the interictal SPECT. The better spatial resolution of PET over SPECT also contributes to an enhanced predictive value of the PET scan. Ictally, there is a parallel increase in both regional cerebral blood flow and metabolism, with nearly 300% increase in the blood flow during a seizure.^{19,20} This reflects into the characteristic area of hyperperfusion in the region of the epileptogenic focus seen on the ictal SPECT scan and a similar area of increased metabolism on the ictal PET.

Indications for Functional Imaging

Although PET and SPECT have been widely studied in temporal lobe epilepsy (TLE), their main contribution is probably in individuals with extratemporal lobe epilepsy. Patients with epilepsy and normal structural imaging (nonlesional epilepsy) can also benefit from functional imaging. In a study performed at a tertiary referral center, an underlying structural cause for chronic epilepsy was found in only 254 of 341 (74%) of the patients.²¹ These results suggest that the number of patients with no structural abnormality on the MRI is significant and, in them, functional imaging can contribute to identify a possible epileptogenic focus.

In the presence of a clearly localized focus in both interictal and ictal EEG recordings consistent with the clinical features on video telemetry and the MRI findings (for instance, an isolated area of hippocampal sclerosis), there is no real indication for nuclear medicine. Nuclear medicine can help in lateralizing or localizing the epileptogenic focus in patients with normal MRI and when imaging is discordant with electrophysiology. If functional imaging detects a possible epileptogenic focus, further evaluation with invasive EEG monitoring for surgical planning is normally necessary, if surgery

is contemplated. The abnormality detected on ictal SPECT and/or FDG-PET can be used as a guide for placement of the subdural EEG electrodes.

Nuclear medicine can also help to localize the epileptogenic focus in the case of bilateral structural abnormalities on MRI, such as in tuberous sclerosis: in this case, the isotope study can show if any of the existing tubers is epileptogenic.

Possible indications for nuclear medicine in the evaluation of drug resistant epilepsy can be summarized as follows: (1) focal epilepsy with normal MRI; (2) in a setting of discordant results between the MRI and EEG; and (3) bilateral lesions on MRI.

Regional Cerebral Blood Flow SPECT Study

Metabolic needs of the brain are met by glucose consumption. The brain does not have the capacity to store large quantities of glucose; therefore, a constant glucose delivery guaranteed by a satisfactory perfusion is necessary. The activated brain cells need more glucose for their increased metabolism; therefore, the blood supply will have to increase accordingly. Brain perfusion and metabolism are therefore coupled during a seizure. The normal tracer distribution in a regional cerebral blood flow SPECT study shows a symmetric pattern of tracer uptake between the two cerebral hemispheres. Prominent uptake is normally noted in the visual cortex of the occipital lobe, especially if the eyes of the patient are open.

Patient Preparation for an Interictal Brain SPECT Study

An intravenous line should be placed several minutes before tracer injection. The patient should lie supine on the gamma camera couch, and the gamma camera room should be quiet with dimmed lights. If the patient has to be sedated or given general anesthesia, this will have to be administered as appropriate before tracer injection.

Data Acquisition and Processing

A high-resolution collimator or a fan beam collimator (which can increase sensitivity by approximately 1.5 times) are recommended. The camera should come very close to the patient's head. The main goal is to achieve the best-possible compromise between the number of counts acquired (sensitivity) and spatial resolution. The variables in the pursuit of this goal are the tracer dose injected, the collimator used, the pixel size, the number of projections, the acquisition time, and the filtering. The data should be reconstructed after re-orientation parallel to the anterior-posterior commissure line. It is also very useful to have another set of data with reconstruction parallel to the long axis of the temporal lobe. Images should be displayed using a continuous color scale. A discontinuous color scale may overestimate tiny asymmetries.

Radiopharmaceuticals

The first tracers used in brain SPECT study were the iodinated compounds, that is, ¹²³I-iodoamines.²²⁻²⁴ ¹²³I-iodoamphetamine is a lipophilic tracer with a high extraction

fraction (greater than 95%) from the bloodstream. This tracer shows a linear relationship between uptake and cerebral blood flow in the high flow range, with a peak activity reached at approximately 20 minutes and 6% to 9% of the injected dose taken up by the brain. The disadvantage of this tracer is the requirement of a cyclotron for the production of ^{123}I . As a result, iodoamines are not widely available. In the mid-1980s, with the advent of $^{99\text{m}}\text{Tc}$ -hexamethylpropyleneamineoxime (HMPAO)^{25,26} and its novel mechanism of uptake, SPECT became more available to study the regional cerebral blood flow in the ictal and interictal periods. The extraction fraction of HMPAO is approximately 80% at first pass. HMPAO crosses the blood–brain barrier (BBB) by passive diffusion with rapid tracer uptake within the brain. Brain activity reaches its peak 1 to 2 minutes after tracer injection. A total of 4% to 7% of the injected dose remains in the brain. After the early prompt uptake, there is a rapid wash out of approximately 15% of the brain activity within the following 10 to 15 minutes. The remaining activity is trapped within the brain via an intracellular oxidation of HMPAO by glutathione, which fixes the HMPAO inside the neurons and glial cells. HMPAO is highly unstable in vitro and it rapidly decomposes in to a hydrophilic compound, which does not cross the blood brain barrier. $^{99\text{m}}\text{Tc}$ -HMPAO must be used within 20 to 30 minutes of its preparation. Stabilized forms of HMPAO have been synthesized, and they provide an improved image quality with less background activity.

$^{99\text{m}}\text{Tc}$ -ethylene cysteine dimer (ECD) is another lipophilic cerebral blood flow tracer. Its extraction fraction is slightly inferior to HMPAO at 60% to 70% and, therefore, it underestimates regional cerebral blood flow at high flow rates. Brain uptake is however slightly greater than HMPAO at 6% to 7% of the injected dose, occurring between 1 and 2 minutes, with lack of back diffusion.^{27,28} Blood clearance is more rapid than $^{99\text{m}}\text{Tc}$ -HMPAO because of the significant renal clearance. Clearance from the brain is very slow (approximately 6% per hour). Once in the brain, ECD is transformed in to a hydrophilic compound that cannot diffuse back through the BBB. The radiation burden from $^{99\text{m}}\text{Tc}$ -ECD is lower than $^{99\text{m}}\text{Tc}$ -HMPAO, because of the rapid renal excretion; it is therefore possible to administer higher doses of $^{99\text{m}}\text{Tc}$ -ECD. The gray-to-white matter ratio with $^{99\text{m}}\text{Tc}$ -ECD is approximately 4:1, in comparison to 2.5:1 with $^{99\text{m}}\text{Tc}$ -HMPAO. $^{99\text{m}}\text{Tc}$ -ECD is stable in vitro (the tracer is usable up to 4-6 hours after preparation) and this is certainly an advantage especially in ictal studies when it is not known when the patient will fit. There has been some debate over the use of the 2 agents, and studies of direct comparison have produced contrasting results. The chemical stability of ECD has led to an increased use of this agent in imaging epilepsy.²⁹⁻³³

The most commonly used (and widely available) PET tracer in epilepsy is FDG. A number of other tracers are in use to image functions like neurotransmitter synthesis, transport, and receptor binding using PET. Other tracers used in epilepsy are [^{11}C] flumazenil (FMZ), which binds to GABA_A receptors, and alpha-[^{11}C]methyl-l-tryptophan (AMT), which is used in children with tuberous sclerosis for epilepsy surgery evaluation.

Other PET tracers with the potential for detecting epileptic brain regions include radiolabeled ligands that bind to opiate receptors, histamine H₁ receptors, monoamine oxidase type B enzyme, N-methyl-d-aspartate receptors, peripheral-type benzodiazepine receptors, and serotonin 1_A receptors. These tracers, although potentially very interesting, are still under evaluation and their role in epilepsy surgery is at present undetermined.

Principle of Brain Perfusion SPECT

The unique characteristic of regional cerebral blood flow tracers is their capacity to identify the epileptogenic focus during a seizure by showing a focal area of significantly increased perfusion (and, consequently, tracer uptake), which corresponds to the epileptogenic focus. As these tracers are trapped within the brain, the SPECT image represents the regional cerebral blood flow during the seizure, though the image is acquired after the seizure. Knowledge of the timing of tracer injection before an ictal SPECT scan is essential for proper interpretation of the images. With an injection at the very onset of a seizure, there is an increased probability of visualizing an epileptogenic focus seen as a focal area of increased uptake. In the event of a delayed injection, the probability of capturing the epileptogenic focus is decreased as the seizure will have already propagated; the ictal scan may then show several areas of slightly increased tracer uptake corresponding to areas of electrical discharge during seizure propagation. The duration of the seizure is also important: it is difficult to capture short-lived seizure with SPECT, as it is likely that the electrical discharge will have already propagated to the remainder of the brain when the tracer reaches the brain cells. In this case, the SPECT findings may be those of widespread hyperperfusion or of different focal areas of increased uptake in the regions where the seizure has spread. Also, each epilepsy subtype shows a different pattern of spread, which translates into different patterns of ictal hyperperfusion on the SPECT scan.

Acquisition of the Ictal and the Interictal SPECT Scans

The Multidisciplinary Team. Imaging epilepsy with nuclear medicine requires a highly specialized set up with a multitask multidisciplinary team.³⁴ It is advisable not to perform such studies at centers that do not have the necessary set up for proper imaging acquisition and interpretation. The epilepsy multidisciplinary team includes a neurologist with special interest in epilepsy, a neurosurgeon specialized in epilepsy surgery, an electrophysiologist, a neuroradiologist, a nuclear medicine specialist with expertise in ictal SPECT and interictal FDG-PET, psychologist and psychiatrist with an interest in pediatrics, telemetry technicians, and a nurse trained in radioisotopes administration. Furthermore, a nurse trained in sedation and the support of an anesthetist is essential. Interpretation of the SPECT and PET in light of other noninvasive tests such as MRI and EEG telemetry at the multidisciplinary meeting is helpful for appropriate patient management.

Technical Aspects. Patients are admitted in hospital for 5 days of continuous video and EEG monitoring. The ictal and interictal SPECT scans are planned during the same admission, with a gap of 48 hours in between. The preparation for the SPECT scan begins with an informed consent from the parents. The injection of the tracer is given in the telemetry suite. The radiopharmaceutical comes in a lead-shielded syringe, which contains the prescribed dose. A vial in a lead pot with a further amount of the radiopharmaceutical is also available so that the necessary dose of tracer can be withdrawn to replace the tracer already decayed in case a significant period of time elapses before a typical seizure occurs. With the exponential decay of the tracer, the dose needs to be readjusted depending on the time elapsed since the preparation of the tracer. A decay sheet is provided with an appropriate volume of tracer to be withdrawn in the syringe every 30 minutes to replace the decayed tracer.

It is preferable to select a typical seizure by observing the patient on the ward and/or looking at the video monitoring before the injection of the tracer to appreciate the semeiology of the seizure selected for the SPECT study. The SPECT scan obtained after injecting on a typical event is likely to represent the regional cerebral blood flow distribution during a typical seizure. In case a seizure has not been captured before the planned time of tracer injection, patient/parent consent is sought to temporarily withdraw either partially or completely all antiepileptic medications to induce seizures. After a successful injection of the tracer, the antiepileptic drugs are re-instituted immediately.

The exact time of tracer injection is noted, together with the time of the EEG onset of the seizure. The time of the tracer injection is time-locked to the EEG recording so that the time lag between the actual injection and the electrographic onset of the seizure can be calculated. This time lag is used to label the tracer injection as ictal, peri-ictal, or postictal. Ictal studies are obtained when the tracer is injected during the clinical manifestation of the seizures. Postictal studies are obtained after an injection administered after completion of a seizure. The term peri-ictal is used to indicate cerebral flow studies when the injection is given between the ictal and the early postictal phase. Knowledge about the timing of the tracer injection in relation to the clinical and EEG onset of the seizure is essential for the interpretation of the ictal scan.

The child is then prepared for the acquisition of the SPECT scan. Sedation is normally given in children aged 1 to 4 years. Children younger than 1 year of age are fed and wrapped before the scan and sedation is rarely used. In the authors' experience, cooperative children older than 4 years of age undergo a SPECT scan with no pharmacological help. Uncooperative children and children with persistent seizures may need general anesthesia, according to the judgment of the consultant neurologist responsible for the care of the child.

If sedation is necessary, it is best given on the ward, before coming to the nuclear medicine unit. An efficient liaison between the neurology ward and the nuclear medicine unit with regard to the time of sedation and the available slot for the scan is essential. One of the commonest causes of a failed ictal SPECT study is a failed sedation. If this happens and a

top up is still insufficient, the scan is abandoned and may be rebooked with the child under general anesthesia. For a complete description of the acquisition and processing of the ictal and interictal SPECT scans, a number of recently published articles are available.³⁵⁻³⁷

It may be difficult to acquire a successful SPECT scan in children. Pediatric epilepsy can be catastrophic with frequent, daily seizures, which may interfere with the acquisition of a good interictal scan. Additionally, a high proportion of children with refractory epilepsy have comorbid issues like learning difficulties and behavioral problems, which may interfere with an accurate identification of the seizure onset and result in a delayed injection of the tracer. Lastly, in the pediatric population, the proportion of extratemporal epilepsies is substantial when compared with adults. Extratemporal seizures are usually of short duration with a rapid spread; hence, a delayed injection may show the spread of the seizure rather than the epileptogenic focus. Such factors may limit the clinical utility of SPECT in pediatric presurgical evaluation. For a comprehensive review on the subject, the following work is recommended.^{27,38-41}

Perfusion Patterns on Ictal SPECT

The epileptogenic zone is observed as an area of hyperperfusion on the ictal SPECT scan. This area is often surrounded by a zone of hypoperfusion that becomes more prominent at the end of the ictal phase (postictal pattern of cerebral blood flow). The reason for this adjacent area of hypoperfusion on the ictal SPECT is unclear. Some authors consider it to be a steal phenomenon explained by the highly increased cerebral blood flow in the seizure focus leading, as a consequence, to a relatively reduced blood flow in adjacent areas; others feel that this area acts like an inhibitory zone limiting the spread of the epileptogenic focus.⁴² The time of the switch from the ictal phase to the postictal phase varies, and with it the duration of the postictal phase.

A successful injection early in the seizure usually gives the best results with a clear localization of the ictal onset zone seen as the most prominent area of hyperperfusion. Injections given late into the seizures may fail to localize the epileptogenic focus and/or may show areas with uptake of variable grade, related to the spread of electrical discharge from seizure propagation. Propagation is often from posterior (parieto-occipital lobes) to anterior cerebral regions (mainly to the temporal and frontal lobe) as shown by Lee and coworkers.⁴³ Another propagation pattern is from the temporal to the frontal lobe. Noachtar and coworkers reported seizure propagation in 85% of parieto-occipital epilepsy. The propagation patterns have been described in a number of studies.⁴⁴⁻⁴⁶ Subtraction of the interictal SPECT from ictal and coregistration of the result with MRI (SISCOM) is best for studying propagation patterns; this technique enhances the sensitivity and spatial accuracy of the ictal SPECT. Using variable thresholds of subtraction a better understanding of the propagation patterns can be obtained. Clinical scenarios like seizures with frontal lobe semeiology in a child with a temporal lobe structural lesion may be explained by studying

the propagation pattern, thus obviating the need for invasive investigations.

Knowledge of the clinical features of the particular seizure captured for the SPECT scan, of the time of the injection in relation to seizure onset, of the ictal and interictal EEG findings, as well as the MRI findings, is essential for a proper interpretation of the SPECT scan features. Discussion at the multidisciplinary team meeting with integration of data from the MRI, EEG, and SPECT/PET, is optimal for an accurate identification of the seizure focus and possibly for surgical planning.⁴⁷

Role of Interictal SPECT

The tracer injection for the interictal scan is administered in the nuclear medicine unit when the patient has not had a seizure for at least 30 minutes. For the interictal scan, the child is taken to the nuclear medicine unit for injection of the tracer. If required a properly trained nurse sedates the child as a preparation for the acquisition of the SPECT scan. General anesthesia may be necessary for slightly older children who may not cooperate for the scan or in whom the level of sedation is deemed to be insufficient.

On its own, the interictal scan has a low sensitivity in the identification of an epileptogenic focus. During the interictal phase, the epileptogenic zone normally shows reduced cerebral blood flow and is seen as an area of hypoperfusion on the interictal SPECT scan. However, occasionally the epileptogenic focus may show normal tracer uptake. Individual variability is possible, with different degrees of hypoperfusion. An area of hypoperfusion is commonly seen in TLE: it involves the anterior pole of the temporal lobe and the mesial temporal region but it can extend into the frontal lobe and the occipito-parietal cortex.

The clinical value of the interictal scan is limited by the little difference between the normal and the hypoperfused areas. Used on its own the sensitivity of the interictal SPECT for detecting an epileptogenic focus does not exceed 50%.⁴⁸ The principal role of the interictal SPECT is to aid the localization of the seizure focus by comparison to the ictal scan, either visually or with subtraction of the interictal from the ictal images.

Statistical Parametric Mapping

SPM compares an ictal SPECT scan to a series of normal regional cerebral blood flow SPECT studies with the aim to identify regions of significant increase in the regional cerebral blood flow, indicative of seizure activity. The voxels within each scan are analyzed with univariate statistical tests to identify regions of significant change in perfusion pattern. Studies have provided evidence for the utility of SPM over visual analysis.⁴⁹⁻⁵¹ One important advantage of SPM is that it can obviate the need of an interictal scan, with the resulting reduced radiation exposure. Inherent disadvantages include false localization caused by regional alterations in cerebral blood flow unrelated to seizure activity, technical factors in image processing that may induce artifacts, and the developmental stage/maturation of the brain with poor localization of the epileptogenic focus in children under 6 years of age.⁵² The results of SPM should be interpreted in the light of the

clinical information available and of possible technical pitfalls during acquisition and coregistration.

Subtraction Ictal Spect

Images and Co-Registration With MRI

Even in the hands of an experienced observer, visual interpretation of the ictal and interictal SPECT scans can be difficult, particularly in patients with extratemporal or nonlesional epilepsy. A quantitative technique such as SISCOM may be able to overcome this difficulty. With SISCOM, the first step involves the coregistration of the ictal and interictal SPECT images by matching surface points of each scan. The scans are then normalized. The transformed interictal scan is subtracted from the ictal scan. The subtraction image shows only those pixels whose intensity is above a set threshold. The image is then coregistered with the MRI after matching the cerebral surface to give an anatomical correlate.

SISCOM enhances the sensitivity and specificity of the ictal SPECT. In some studies, the probability of localizing an epileptogenic focus was greater with SISCOM than with the ictal EEG and MRI.⁵³⁻⁵⁶ In a particular study, the final registered images prompted the radiologist to review the MRI scan, which showed a subtle area of cortical dysplasia in the parietal lobe in one patient previously reported as normal.⁵⁷ Similarly, in another study the MRI scans of 6 patients were reviewed after the result of the SISCOM analysis, and the initial normal report was changed as subtle abnormalities were identified at the same site of the abnormalities identified by SISCOM.⁵⁸ In the same study, the authors showed good surgical outcome when the site of surgery and the focus localized by SISCOM were concordant and poor outcome with discordant SISCOM focus and resection site.^{53,55} A study by Kaminska and coworkers showed that in 20 pediatric cases the final coregistered SISCOM image localized to the area of resection in 70% of the cases with good outcome.⁵⁹

SISCOM can help surgical planning in dysembryoplastic neuroepithelial tumor (DNET). In fact in a number of patients with DNET there is a surrounding area of cortical dysplasia not visible on MRI and that has to be removed to obtain good surgical outcome. With the use of SISCOM this area of cortical dysplasia is better highlighted.⁶⁰ Studies in children have demonstrated the added clinical value of SISCOM over the ictal or interictal SPECT alone.^{61,62} Image coregistration allowed the detection of at least one hyperperfused focus in 93% of children, compared with 74% using ictal and interictal scans separately.

However, even with SISCOM, technical factors such as a delayed injection or problems in coregistration may adversely affect the localization of the epileptogenic focus. Potential pitfalls also include false lateralization of the epileptogenic focus in cases of TLE and visualization of the seizure spread rather than the epileptogenic zone.

Positron Emission Tomography

General and Technical Aspects

A number of PET tracers are in use; they visualize different functions in the brain, namely cerebral blood flow, glucose metabolism, protein synthesis, neurotransmission, and neu-

roreceptor density. Because children are quite different from adults, expertise in dealing with them is important.⁶³

A PET scan can be analyzed visually or quantitatively. Quantitative analysis can be used as an adjunct to visual analysis. A simplified method to quantify cerebral glucose utilization in early infancy was published by Suhonen-Polvi and coworkers.⁶⁴ If blood samples cannot be obtained, standard uptake value (SUV) represents an alternative for estimation of cerebral glucose uptake and, thus, for interindividual comparison of patients.

The findings of the FDG-PET scan may be confusing if the patient has a seizure close to the time of the scan. EEG monitoring at the time of the PET scan is normally performed to capture possible clinical or subclinical seizures that may occur during the FDG uptake period and may explain some of the findings on the PET scan.

An FDG-PET scan performed to localize a seizure focus is acquired in the interictal state. Rapid changes in glucose metabolism as they occur in the ictal state cannot be studied with the PET scan as it takes 30 to 40 minutes for the tracer to be taken up by the brain.

Antiepileptic drugs have been shown to decrease cerebral glucose metabolism globally; this effect is most marked with barbiturates, less so with sodium valproate and least with phenytoin and carbamazepine.

FDG-PET has been shown to be more sensitive than MRI in the identification of seizures of temporal lobe origin.⁶⁵ FDG-PET is also valuable in patients with intractable epilepsy without a structural lesion. In this group of patients, FDG-PET shows an area of hypometabolism that may correspond to a localized focus on the EEG. In patients with TLE and normal structural imaging, FDG-PET adds lateralizing and localizing information in nearly 60% of cases.⁶⁶ This information can be used to carry out invasive EEG monitoring for further characterization of the focus.

A weakness of FDG-PET is the failure to identify an epileptogenic focus in 10% of temporal lobe seizures with a hippocampal sclerosis on MRI.^{67,68} Also subclinical electrographic activity in deeper structures may falsely elevate glucose metabolism, leading to false lateralization.

Focal Seizures of Temporal Lobe Origin

TLE can be either mesial or lateral. Mesial TLE is caused by hippocampal pathology characterized by neuronal loss and gliosis. In lateral (neocortical) TLE, structural lesions such as tumors, vascular malformations, and cerebral dysgenesis are common pathologies. Most of these abnormalities are detected on MRI; however, in a number of patients with refractory epilepsy, structural lesions are not visible on MRI (nonlesional or cryptogenic epilepsy). Seizures of lateral temporal origin may not have the classic features of TLE, such as oral or motor automatism, but may present with visual and auditory auras. Because these 2 types of epilepsy require a different surgery and have different outcomes, differentiation between them is essential.

The most common pathology in adult TLE is mesial temporal sclerosis (MTS), but in pediatric TLE the pathology is

equally divided among focal cortical dysplasia, developmental tumors, MTS, and dual pathology (for example, MTS and focal cortical dysplasia).

PET in TLE

Patterns of FDG Uptake. The usual FDG-PET finding in TLE is hypometabolism of the ipsilateral temporal lobe with or without less severe hypometabolism in the extratemporal structures like frontal lobe, parietal lobe and also, occasionally, the contralateral temporal lobe. In lesional epilepsy the area of hypometabolism is normally greater than the extent of the structural lesion.⁶⁹ There are instances when the FDG-PET scan is normal and such a scenario is seen only in non-refractory cases of TLE.

Interictal FDG-PET reveals focal temporal lobe hypometabolism in 85% of cases with refractory TLE but with quantitative analysis this may increase to 90%.⁷⁰ The area of hypometabolism in the temporal lobe corresponds anatomically to the areas localizing epileptogenicity as shown by in-depth electrodes.⁷⁰ On FDG-PET it is difficult to differentiate mesial from lateral TLE as mesial TLE may show glucose hypometabolism extending to the lateral aspect of the abnormal temporal lobe.⁷¹ Quantitative studies in mesial TLE have demonstrated severe hypometabolism in the anterior mesial structures including the amygdala and the hippocampus either limited to these structures or more prominent in them than in the lateral structures^{72,73}; these features suggest that the hypometabolism visible in the lateral structures may be nonreal and possibly due to a partial volume effect.

In mesial TLE it is possible to see hypometabolism in the contralateral temporal lobe but to a lesser extent than in the affected ipsilateral temporal lobe. Widespread hypometabolism involving the entire temporal lobe and ipsilateral frontal, parietal lobes, and occasional hypometabolism of the contralateral temporal lobe with subcortical involvement of the thalamus and basal ganglia is also seen, but is relatively uncommon.⁷⁴ Even within this widespread area of hypometabolism there are subtle differences, with more severe hypometabolism in the temporal lobe and less severe in the extratemporal structures. This wide area of hypometabolism within the ipsilateral hemisphere and at times in the contralateral hemisphere may represent the epileptogenic network involved in the spread of the seizures. It has been postulated that this widespread hypometabolism might be related to behavioral and neuropsychological dysfunctions seen in the interictal period.⁷⁵ In a pediatric series of 16 patients with partial seizures,⁷⁶ only one child showed subcortical hypometabolism; this may be related to the duration of epilepsy, with epilepsy of shorter duration not showing the widespread hypometabolism. In the same study nearly 70% of children with normal MRI showed evidence of hypometabolism.

FDG-PET Findings and Extent of Surgical Resection. The question arises whether the entire hypometabolic region needs to be resected. A study by Juhasz and coworkers⁷⁷ showed that, although FDG-PET abnormalities localized to the epileptogenic area, the extent of resection did not alter

surgical outcome; however, they found a significant relationship between the extent of resection and the area of abnormality on ^{11}C -FMZ PET. Extensive cortical abnormalities on FMZ PET were associated with poor outcome following neocortical epilepsy surgery; resection of the FMZ abnormalities was associated with an excellent outcome even in the absence of a structural lesion.

Ollenberger and coworkers⁷⁸ performed a survey on the impact of FDG-PET on the diagnosis of epilepsy and surgical decision-making in 114 children younger than the age of 14 years. The survey found additional information from FDG-PET on the epileptogenic zone in 77% of the cases; FDG-PET scan had a major impact on surgical decision making in 51% of the cases.

Pre- and postoperative FDG-PET scans in patients who underwent temporal lobectomy for mesial TLE have shown significant differences, with decreased postoperative FDG uptake in the caudate nucleus, the pulvinar, fusiform gyrus, lingual gyrus, the posterior region of the insular cortex in the hemisphere ipsilateral to resection, and increased postoperative FDG uptake in the anterior region of the insular cortex, temporal stem white matter, midbrain, inferior precentral gyrus, anterior cingulate gyrus, and supramarginal gyrus ipsilaterally. It has been proposed that focal increase in glucose metabolism postoperatively may represent the propagation pathways of ictal and interictal epileptic discharges in mesial TLE; on the other hand, the postoperative decrease in glucose metabolism may be related to a permanent loss of afferents from resected anterior-mesial temporal structures.⁷⁹ Areas of hypometabolism remote from the epileptogenic focus can be occasionally seen on a FDG-PET scan; after surgery the same areas show normalization of glucose metabolism. The reason for this may be a metabolic inhibition by the intercortical pathways, released after surgery.⁸⁰

Pathological Substrate to FDG-PET Findings. The cause of glucose hypometabolism interictally is still under speculation. It has been postulated that atrophy of the cortex with neuronal loss and secondary changes, caused by the developed epileptogenic networks (otherwise called diaschisis), may explain the hypometabolism⁸¹; however, a study with quantitative FDG-PET in patients with TLE contradicts this hypothesis.⁸² The resected temporal lobe specimens from the patients who underwent surgery showed a normal neuronal density at pathology and yet hypometabolism in the same temporal lobe on the preoperative FDG-PET scans.⁸²⁻⁸⁴ The cause of the hypometabolism may therefore include other factors in addition to the ones already considered, such as the proximity of a seizure to the time of the PET scan, as the epileptogenic cortex is expected to be hypometabolic in the postictal period. At present, none of the hypotheses for a cause of the observed macro- and microstructural changes observed in TLE fully explains the reason of hypometabolism.

In a series of 126 children with TLE, only 10 patients were investigated with FDG-PET, which revealed hypometabolism in 70% of the scans.^{85,86} In the remainder of the patients, the PET scan was normal, with a few odd reports of interictal

hypermetabolism. It has been suggested that in these patients there is a continuous but subclinical epileptiform activity not picked up on routine interictal scalp EEG recordings. This activity tends to increase glucose cerebral metabolism with either a corresponding hypermetabolism or an apparent normalization of both temporal lobes on the FDG-PET scan. Interpretation of FDG-PET in such circumstances can be very difficult.

When compared to patients with unilateral temporal lobe hypometabolism, patients with bilateral temporal lobe hypometabolism had a greater percentage of generalized seizures; they were more likely to have bilateral, diffuse, or extratemporal seizure onset and had bilateral or diffuse MRI abnormalities.⁸⁷ In the same study, 10% of patients had bilateral glucose hypometabolism. Patients with bilateral temporal lobe hypometabolism have a worse prognosis for seizure remission after surgery.^{87,88} Several studies have indicated that patients with mesial temporal hypometabolism on PET imaging have a greater probability of being seizure free postoperatively than patients with hypometabolism in other parts of the temporal lobe.⁸⁹

FDG-PET is more sensitive than MRI in the identification of the seizure focus in TLE. A number of studies in the adult population show the benefit of PET in TLE with normal MRI. Similar results have been reported in pediatric surgical series with normal MRI imaging.⁷⁶

The use of SPM analysis for the interpretation of PET scan in TLE was shown to be nearly as comparable to the visual analysis by an experienced nuclear medicine specialist.⁹⁰ An article by Casse and coworkers tested FDG-PET and ictal SPECT in 21 children with TLE. FDG-PET correctly localized epileptogenic zones in 20 of 21 (95%) by visual assessment and SPM analysis of FDG-PET correctly localized epileptogenic zones in 18 of 21.⁸⁸

Ictal SPECT in TLE

An ictal regional cerebral perfusion study with SPECT provides correct localization of the epileptogenic focus in 80% to 90% of cases with unilateral TLE and incorrect localization in 2% of cases.⁹¹ Ictal SPECT in TLE is useful when the MRI is normal or when the EEG findings are discordant from the MRI result. In TLE with MRI and EEG concordant among themselves and in agreement with the clinical features on video telemetry, a nuclear medicine scan is usually not necessary. Seizures originating from the temporal lobe have shown different patterns of hyperperfusion on ictal SPECT depending on their origin, either mesial or lateral. Ho and coworkers^{92,93} studied TLE patients with ictal SPECT and divided TLE into 4 groups based on pathology. The groups with hippocampal sclerosis and other lesions in the mesial temporal lobe showed well-localized areas of hyperperfusion involving the ipsilateral mesial and lateral temporal regions. Lesions within the lateral temporal lobe tended to show asymmetric bilateral changes with more significant hyperperfusion on the ipsilateral side. The MRI negative group with good surgical outcome showed a pattern of hyperperfusion restricted to the ipsilateral antero-mesial temporal structures.

These different patterns of perfusion have been explained

on the basis of seizure propagation, for instance, the bilateral hyperperfusion can be explained on the basis of connections between the lateral temporal cortex and the opposite amygdala through the anterior commissure.

The timing of the tracer injection is relevant to the area of hyperperfusion. In the context of mesial TLE, an injection of the tracer within 15 seconds from seizure onset shows a marked hyperperfusion of the whole temporal lobe and may be accompanied by hypoperfusion of the surrounding structures like the ipsilateral orbital cortex, the ipsilateral frontal lobe or the ipsilateral hemisphere.^{94,95} A slightly delayed injection, or peri-ictal injection, will show hyperperfusion in the lateral temporal cortex, orbital cortex, basal ganglia, motor cortex, or generalized uptake, or may even show bitemporal uptake; these features are related to the spread of the seizure. At the end of the ictal discharge (within 4 minutes from the end of the seizure) there is marked hypoperfusion of the lateral temporal lobe and with time the area of hypoperfusion extends to the ipsilateral frontal lobe and occasionally to the contralateral hemisphere. The mesial structures continue to remain hyperperfused during these 4 minutes and then start showing isoperfusion relative to the contralateral structures until 15 minutes from the end of the ictal discharge; eventually, the mesial structures also show hypoperfusion. The postictal area of hypoperfusion gradually increases in size as time goes by, to involve the entire ipsilateral temporal lobe. Therefore, a delayed tracer injection may show the spread of seizures from the temporal lobe to the ipsilateral basal nuclei, the basal frontal lobe, or a generalized increase in tracer uptake, depending on the spread of the seizure.

The typical perfusion patterns of markedly increased uptake in the homolateral temporal lobe seen with an early injection (Fig. 1), or the bilaterally increased uptake, or the temporal hyperperfusion with posterior extension, have all been shown to have a relatively good postsurgical outcome with 60%, 67%, and 69% seizure free outcome.⁹³

As in adults, ictal SPECT plays a similar role in localization of epileptogenic focus in pediatric TLE.⁹⁰ In a series of 126 children who had temporal lobectomy, SPECT was performed in 39 children; 25 (64%) scans showed localized hyperperfusion in the ipsilateral temporal lobe and another 4 (10.2%) scans showed ipsilateral hemispheric hyperperfusion.⁸⁵ Another study by Harvey and coworkers⁹⁶ found localizing information from the ictal SPECT concordant with the ictal EEG and MRI in 14 of 15 patients.

Although an ictal SPECT scan with a purely ictal injection is best to visualize an epileptogenic focus, there may be some value in postictal scans. In a study by Rowe and coworkers,⁹¹ 31 of the 45 patients with TLE showed a typical pattern of mesial temporal increased blood flow accompanied by reduced uptake in the lateral temporal lobe, compatible with a unilateral focus on EEG. The positive predictive value for such features was shown to be 97%.

Therefore, a postictal SPECT may be of more value than an interictal SPECT in the majority of cases as the postictal hypoperfusion can last for up to 20 minutes, corresponding to the degree and extent of slow wave activity on the postictal

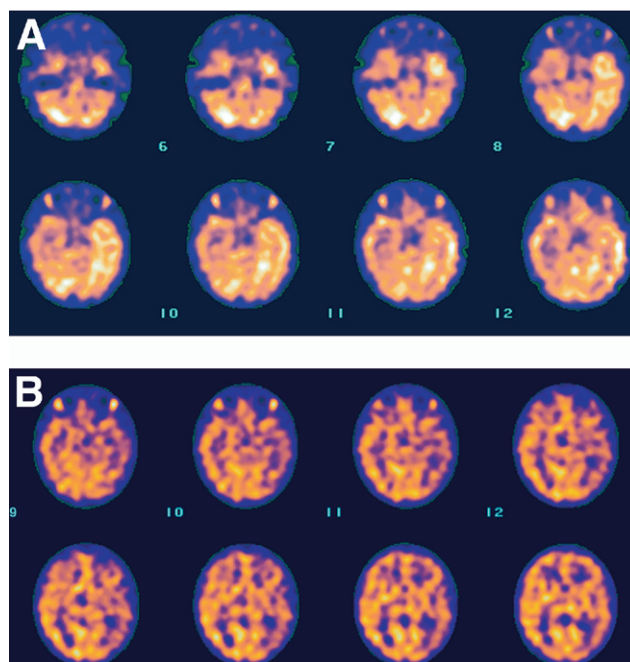


Figure 1 Ictal (A) and interictal (B) SPECT with ^{99m}Tc-ECD in a 6-year-old boy with intractable complex partial seizures. He had 2 types of seizures: smaller seizures, 1 to 3 a day, lasting 30 to 45 seconds each, and bigger seizures, 1 to 5 a day, lasting 2 minutes. The interictal EEG showed slow waves in the left temporal lobe region. The ictal EEG localized to the left temporal lobe, with subsequent generalisation. The MRI scan showed changes in the left temporal lobe, compatible with focal cortical dysplasia. The SPECT injection was 19 seconds into the seizure. The ictal SPECT scan shows a definite area of increased uptake in the left temporal lobe extending to the posterior aspect of the temporal lobe. The interictal SPECT shows reduced uptake in the left temporal lobe. Neuropsychology examination demonstrated that the boy was right handed and his verbal abilities were in the exceptionally low range. Based on the SPECT findings, a maximal temporal lobe resection was performed. The boy is currently seizure free 2 years after surgery. (Images courtesy of Dr. Lorenzo Biassoni, Department of Radiology, Great Ormond Street Hospital for Children, London, UK.)

EEG. In general, ictal tracer injections in mesial TLE show increased tracer uptake in almost all cases. Postictal injections give a sensitivity for the epileptogenic focus of 70% to 90%.⁹¹

Focal Seizures of Extratemporal Lobe Origin

Nuclear medicine has an important role to play in the localization of the seizure focus in patients with intractable extratemporal lobe epilepsy. The proportion of extratemporal epilepsy in pediatric population is greater than the adult population.⁹⁷ Also the proportion of patients with normal MRI in this group is high; these patients therefore require extensive noninvasive and invasive EEG monitoring and functional imaging with radioisotopes, in the attempt to identify an epileptogenic focus. Unfortunately despite the technical advances in the localization of the epileptogenic focus, the results of surgery in this group of patients are not as good as for TLE: only 50% to 60% of patients eventually

become seizure-free.^{97,98} As already mentioned, SISCOM enhances the value of the information available from the ictal SPECT scan. The importance of an early injection after the seizure onset cannot be overemphasized: a delayed injection usually misses the epileptogenic focus, which tends to spread rapidly, and may only capture the spread of the seizure.

PET in Extratemporal Epilepsy

The sensitivity of FDG-PET in detecting areas of hypometabolism in extratemporal (or neocortical) epilepsy is not as great as in patients with TLE. The proportion of normal FDG-PET scans is higher compared with partial seizures with origin in the mesial or lateral temporal lobe.⁸⁸ FDG-PET is also normal in the majority of patients with normal MRI.^{99,100} The main role of FDG-PET in lesional or nonlesional extratemporal lobe epilepsy is to guide the surgeon in placing the subdural electrodes for invasive EEG monitoring. Studies have shown that the hypometabolic area on FDG-PET extends beyond the primary epileptogenic region and therefore cannot define accurately the boundaries of the epileptogenic focus; however, FDG-PET still remains a valuable tool for lateralisation and general localization of the presumed epileptogenic focus.⁷⁷

In patients with extratemporal epilepsy, a positive FDG-PET scan shows an area of hypometabolism with a gradual transition to the surrounding areas of normal glucose metabolism. The duration of the epilepsy is relevant for the results of the PET scan: patients with chronic partial epilepsy show larger areas of hypometabolism when compared with cases of new onset partial epilepsy.¹⁰¹

Frontal lobe epilepsy forms a substantial number of neocortical epilepsies. Normal FDG-PET scans are frequently seen in these patients. In patients with hypometabolism, this may be widespread to include mesial and lateral temporal areas, parietal lobe, and occasionally ipsilateral thalamic and basal nuclei.

Different studies in frontal lobe epilepsy have found the sensitivity of FDG-PET in localizing the epileptogenic zones to be in the range of 45% to 73%.¹⁰²⁻¹⁰⁶ In MRI-negative patients, the sensitivity of FDG-PET was found to be around 36%.¹⁰³ A wide area of hypometabolism precludes an accurate localization of the epileptogenic focus. A particular study on FDG-PET in 13 children with nonlesional frontal lobe epilepsy showed unilateral hypometabolism, which included the frontal lobe in 11 cases; in 8 of them, the area of hypometabolism was confined only to the frontal lobe.¹⁰⁶

As compared with adults, children with frontal lobe epilepsy have a relatively greater number of positive FDG-PET scans. It has been proposed that in neonatal or infantile onset of frontal lobe epilepsy an underlying structural cause is almost always present. This structural cause may not always be visible on MRI therefore the information from the FDG-PET scan is of considerable value in selecting patients for surgery.¹⁰⁶

There have been a few studies evaluating the performance of presurgical evaluation in parietal and occipital epilepsy. In these studies, the specificity and sensitivity of the FDG-PET

scan has been shown to be either similar or quite different from the MRI or SPECT.^{107,108}

Ictal PET has been performed in the setting of extratemporal epilepsy. $H_2^{15}O$ and $^{13}NH_3$ are 2 tracers used to measure seizure activity with ictal PET. They can measure regional cerebral blood flow and oxygen metabolism. Some studies have suggested a role for a planned ictal FDG-PET in individuals with frequent seizures.¹⁰⁹ Comparative studies have shown ictal hypermetabolism in patients having seizures during the FDG-PET study. Engel and coworkers^{20,110} found that the area of hypermetabolism does not necessarily have to correspond to the interictal area of hypometabolism. The intensity of hypermetabolism is related to the difference in time between the injection of tracer and the seizure. During a seizure glucose metabolism may increase to several times from the baseline; this is seen as an area of hypermetabolism on the PET scan.¹¹¹

SPECT in Extratemporal Epilepsy

The most frequent pathology in extratemporal lobe epilepsy is focal cortical dysplasia. The use of ictal SPECT in extratemporal epilepsy is to confirm the epileptogenicity of the visible structural lesion and to localize the area for placement of subdural grids for invasive EEG monitoring. Numerous studies have been performed to compare the success rate of PET, MRI, and SPECT in the identification of the seizure focus. In a report of 117 patients with neocortical epilepsy the success rates of MRI, PET and ictal SPECT were reported as 60%, 78%, and 70%, respectively.¹¹²

Seizures originating in the parietal lobe spread depending on the seizure semeiology; seizures with sensory and motor manifestations often show an anterior spread. Seizures from the occipital lobe propagate quickly to both temporal lobes, necessitating a particularly early tracer injection. In fact in one study of 6 patients with negative MRI ictal SPECT was more sensitive than PET scan in showing the epileptogenic focus.¹¹³ However, another study¹¹⁴ of FDG-PET and ictal SPECT showed a localized occipital focus in 60% of PET scans compared with 29% of ictal SPECT scans.

In frontal lobe epilepsy, ictal hyperperfusion has been demonstrated in various parts of the frontal lobe and also in the ipsilateral basal nuclei; a contralateral cerebellar hypoperfusion was frequently demonstrated (crossed cerebellar diaschisis).¹¹⁵

Studies of DNET in the temporal lobe or in an extratemporal location have shown an associated area of cortical dysplasia surrounding the tumor that is not visible on MRI. In such circumstances, the ictal SPECT may show an area of hyperperfusion wider than the tumor itself; this helps surgical planning.

A limiting factor for a successful ictal SPECT scan in extratemporal seizures is the short duration of the seizures. For an accurate localization, it has been estimated that the seizures originating from an extratemporal focus should last for at least 10 to 15 seconds after tracer injection. Postictal injections are of little value as the perfusion changes caused by the seizure do not extend into the postictal period, as in seizures of temporal lobe origin. Also, a late tracer injection may show

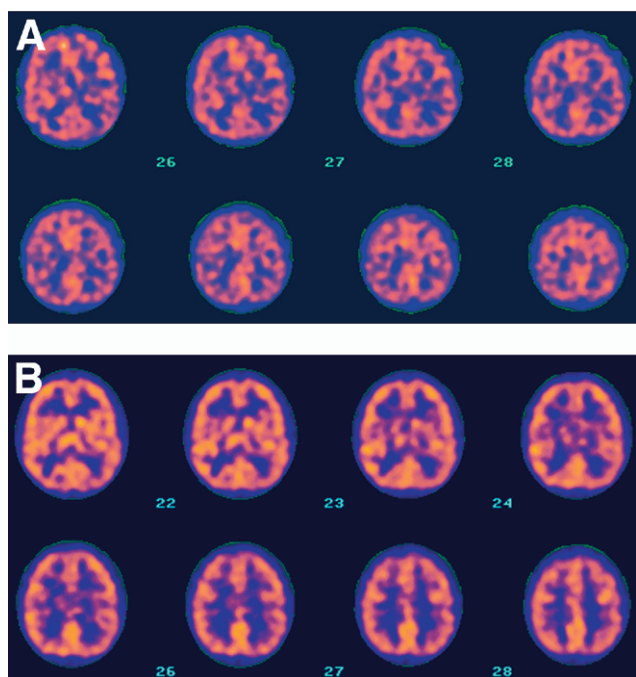


Figure 2 Ictal (A) and interictal (B) SPECT scans in a 10-year-old boy with generalized tonic clonic seizures; EEG findings were compatible with an epileptogenic focus in the right frontal region; the first MRI was reported as normal. The ictal SPECT scan (injection given 17 seconds into the seizure) shows a focal area of increased tracer uptake in the mesial aspect of the right frontal region, just to the right of the midline. The interictal scan shows slightly reduced uptake in that area. A repeat MRI showed a focal area of cortical dysplasia in the right mesial frontal region, corresponding to the focus shown by the SPECT study. The child underwent a right frontal resection and has been seizure free since (at 18-month follow-up). (Images courtesy of Dr. Lorenzo Biassoni, Department of Radiology, Great Ormond Street Hospital for Children, London, UK.)

the spread of the seizure rather than the epileptogenic focus, with multiple areas of hyperperfusion caused by the spread of the electrical discharge.

The utility of SPECT in extratemporal epilepsy is to confirm the epileptogenicity of the structural lesion visible on MRI and to identify the area for placement of subdural grids for invasive EEG monitoring in MRI-negative patients. The role of ictal SPECT is of greater value in the localization of complex partial seizures than in those with simple partial seizures. Ictal SPECT is not particularly helpful in secondary generalized seizures because these demonstrate multiple areas of hyperperfusion. Some examples of ictal SPECT in extratemporal lobe epilepsy are shown in Figures 2 and 3.

Use of Nuclear Medicine After Failed Epilepsy Surgery

Patients with persisting/recurrent epilepsy after surgery constitute a challenging group. Data on the use of nuclear medicine tests after a failed surgical procedure are scarce, probably reflecting the limitations of nuclear medicine investigations in such setting. This limitation is depicted by the fact that interictal FDG-PET may well continue to show hy-

pometabolism in the vicinity of the resected cortex, but the interpretation of this finding is uncertain because it is difficult to distinguish between residual epileptogenic tissue or postsurgical sequelae. There are only a few studies on ictal SPECT (Fig. 4) or ^{11}C -AMT in the postsurgical evaluation of patients with persisting/residual epilepsy. Wetjen and coworkers¹¹⁶ studied 58 patients referred for repeat surgery and used SISCOM with ictal EEG to localize the epileptogenic focus. In 46/58 patients SISCOM revealed a localized area of hyperperfusion, but only in 32/46 was the focus concordant with EEG. Only 50% of those patients who had a concordant SISCOM/EEG focus underwent surgery and had a good outcome. The study by Juhasz and coworkers¹¹⁷ concluded that AMT-PET can identify nonresected epileptogenic cortex in patients with failed surgery for neocortical epilepsy and can assist in planning a repeat surgical procedure. They suggested that the best results are obtained if the scan is performed between 2 and 27 months after surgery. Earlier or later scans did not help with surgical planning in their series.

Use of Nuclear Medicine in Other Seizure Disorders

Infantile Spasms

Infantile spasms constitute an age specific syndrome, which is classified into two main groups, symptomatic and cryptogenic, depending on whether the underlying condition is identified on imaging or not. There is a third small group, named idiopathic infantile spasms, which shows a good response to medical therapy. In these patients, as with the patients in the symptomatic group, the lesion is usually detected on MRI. It is the cryptogenic variety that requires a detailed evaluation with MRI and nuclear medicine to identify a cause for the spasms; once an abnormality is found, a patient diagnosed with cryptogenic infantile spasms is re-classified within the symptomatic group.

Unilateral cortical hypo- or hypermetabolism is frequent in children with infantile spasms. The usual picture is of cortical hypometabolism. Areas of hypermetabolism can be seen and often are correlated to a spiking focus during the FDG uptake period; a simultaneous EEG recording is therefore necessary for a proper interpretation of the PET scan. Definite unilateral hypometabolism in refractory spasms may support surgical management if there is concordance of the EEG focus with the area of hypometabolism. This is associated with a good surgical outcome with complete or partial resolution of the spasms and possibly of the associated developmental delay.¹¹⁸⁻¹²⁰

In the large series of 140 children with infantile spasms reported by Chugani and coworkers,¹²¹ 42 of 140 patients were symptomatic with 29 infants demonstrating structural lesions on MRI. Of the 97 cryptogenic cases in this series, 30 children had unilateral cortical hypometabolism and 62 showed multiple areas of hypometabolism. These 92 patients were re-classified as symptomatic and the number of symptomatic cases rose to 134 (95.7%). The PET scan had an important role in picking up abnormalities not seen on MRI.

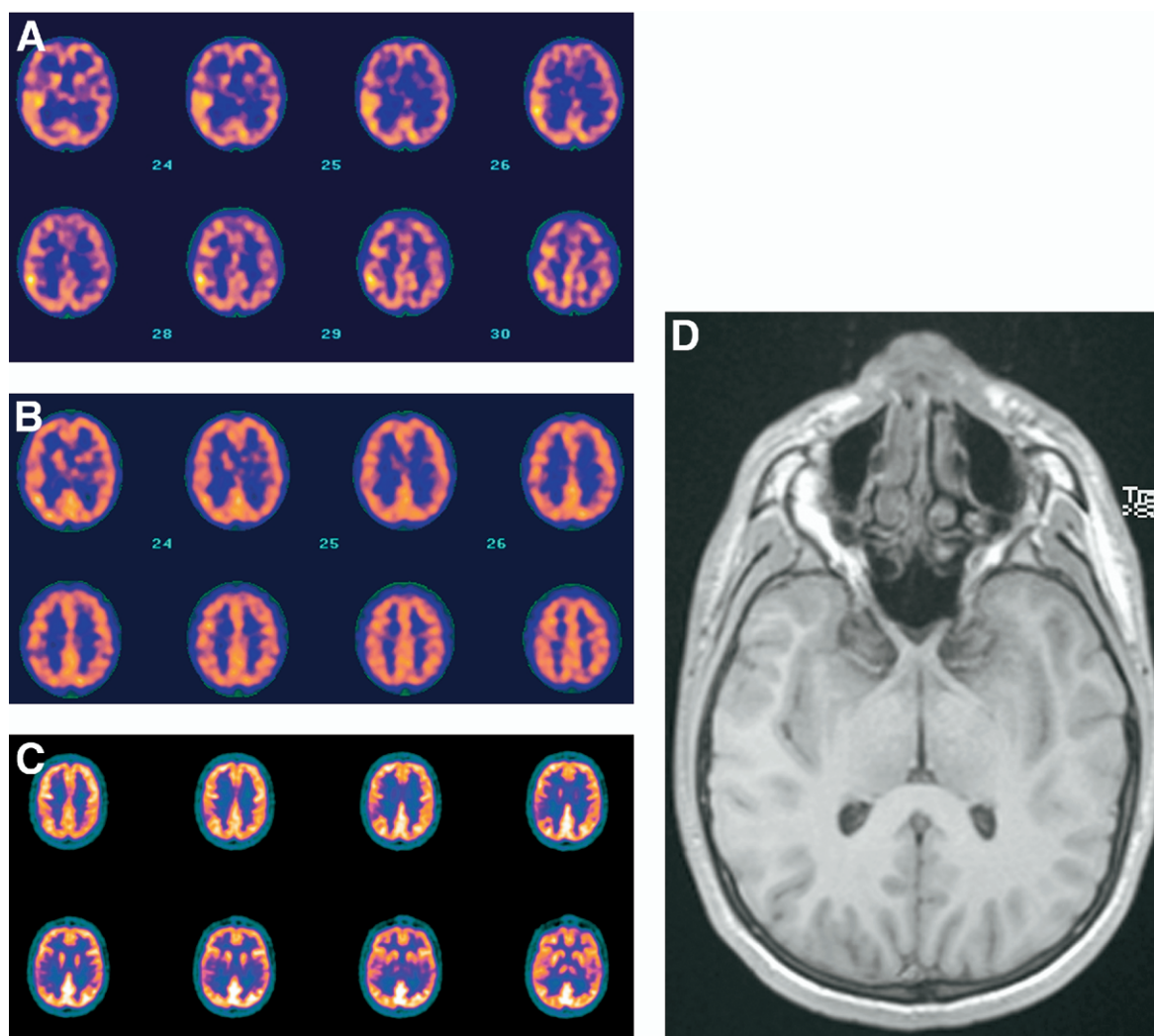


Figure 3 Ictal (A) and interictal (B) SPECT scan together with interictal FDG-PET (C) and MRI (D) in a 16-year-old boy with intractable focal epilepsy. EEG localized a focus of epilepsy in the right parietal region. Ictal SPECT shows a focal area of increased tracer uptake in the right parietal lobe; the interictal scan shows decreased tracer uptake in the same area. The FDG-PET scan shows an area of decreased tracer uptake in the right parietal lobe. The MRI was normal. Following discussion at the multidisciplinary team meeting, it has been decided to proceed to further evaluation with in-depth EEG monitoring in the right parietal region in view of surgery. (Interictal FDG-PET images courtesy of PET Imaging Centre, St. Thomas' Hospital, London, UK; SPECT and MRI images courtesy of the Department of Radiology, Great Ormond Street Hospital for Children, London, UK.)

In infants who had surgery the most common pathology was cortical dysplasia.

A feature seen in approximately 10% to 15% of cryptogenic spasms is the presence of bitemporal glucose hypometabolism. Such infants are not suitable for surgery, and they display a clinical phenotype of developmental delay particularly in the domain of language and autism.

A reason for the low sensitivity of MRI in identifying structural lesions in children with infantile spasms may be the incomplete maturation of the white matter tracts in infancy. This makes the MRI less sensitive to detect nodular heterotopias and other dysplasia as the gray to white matter contrast is poor.¹¹⁸

Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome (LGS) is defined as the presence of multiple seizure types, including atonic, tonic, absence,

and generalized tonic clonic seizures and cognitive impairment with a EEG pattern of slow spikes and waves. The syndrome also includes learning and behavioral difficulties. Some of these patients have had infantile spasms in infancy that evolve into LGS.

LGS may or may not have structural lesions. Symptomatic LGS may benefit from surgery but the cognitive and behavioral impairment is irreversible. The majority of patients with LGS are not suitable for resective surgery, but they may benefit from corpus callosotomy; this can significantly reduce the drop attacks, the most disabling feature of the syndrome.

FDG-PET in LGS usually shows bilateral diffuse hypometabolism, but other patterns like unilateral focal hypometabolism, unilateral widespread hypometabolism, and normal FDG distribution can be seen. The final decision for surgical

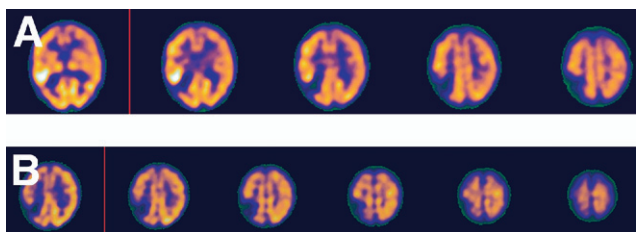


Figure 4 A 12-month-old child with symptomatic focal epilepsy. The first evaluation showed an area of cortical dysplasia in the right parietal lobe extending into the angular gyrus; EEG and SPECT were concordant among themselves and with the MRI. The child underwent resection of the area of cortical dysplasia. However, after surgery, he continued to have seizures. A repeat ictal (A) and interictal (B) SPECT study was performed, which showed a focal area of intensely increased tracer uptake in the right parietal lobe. The child underwent further surgery. After surgery, the child is now seizure free (at 24-month follow-up). (Images courtesy of Dr. Lorenzo Bissoni, Department of Radiology, Great Ormond Street Hospital for Children, London, UK.)

procedure like corpus callosotomy is usually based on the clinical assessment and EEG recordings.

Tuberous Sclerosis

Cortical tubers comprise of simplified dendritic arborizations¹²² and this forms the basis of hypometabolism on the FDG-PET scan. Ictally the same tuber may show hypermetabolism. PET scanning with ¹¹C-AMT is used to measure tryptophan uptake; this can help in the presurgical evaluation of children with tuberous sclerosis (TS). The scan shows an area of increased uptake in the epileptogenic tuber in contrast to the focal hypometabolism seen on FDG-PET. A series of studies^{123,124} have shown that AMT correctly differentiates between epileptogenic tubers, which show increased tracer uptake, and nonepileptogenic tubers, which show decreased uptake. Another study¹²⁵ has shown a good correlation between resection of epileptogenic tubers and postoperative seizure outcome. Though ¹¹C-AMT has improved the management of children with TS, only in about two thirds of cases the AMT scan was positive; in the remainder of the patients there was no evidence of increased AMT uptake. FDG-PET coregistered with MRI with diffusion tensor imaging is probably of use in identifying such epileptogenic tubers.¹²⁶ Larger areas of FDG-PET hypometabolism relative to MRI tuber size and higher apparent diffusion coefficient values better identified epileptogenic tubers and adjacent cortical dysplasia in patients with TS. It has been suggested that this technique used in conjunction with other noninvasive tests significantly contributes toward the presurgical evaluation of children with TS.¹²⁶

Ictal SPECT study is also helpful in patients with TS. A study by Koh and coworkers¹²⁷ showed that the ictal SPECT pattern of focally increased uptake in the epileptogenic tuber usually corresponds to the ictal EEG pattern of sustained rhythmic fast activity. In a sense it may be possible to predict a positive SPECT scan depending on the pattern of ictal EEG. The information from the ictal SPECT may be valuable in presence of multiple tubers (to identify the epileptogenic

tuber) and in the case of nonlateralising or nonlocalising EEG.

Sturge Weber Syndrome

This a neurocutaneous syndrome associated with facial nevus and leptomeningeal angiomatosis. FDG-PET shows hypometabolism ipsilateral to facial nevus and determines the extent of hemispheric involvement. Interestingly in infancy and early life, children with this syndrome may show interictal hypermetabolism in the affected hemisphere; the cause of the paradoxical increased uptake is presumed to be the anaerobic glucose metabolism in the chronically ischemic hemisphere. FDG-PET provides useful information about the extent and degree of hemispheric involvement, essential for surgical planning. The PET scan can guide the extent of resection in uni-hemispheric involvement. Similarly FDG-PET also evaluates the functional integrity of the opposite hemisphere in individuals being evaluated for hemispherectomy and in some cases may reveal contralateral hypometabolism; this may indicate the presence of an additional leptomeningeal angioma, thus excluding such cases from surgery.

Receptor Density Studies

At present, receptor density studies are not routinely used as part of presurgical evaluation. However, such studies may provide valuable insight in the understanding of epilepsy.

Benzodiazepine Receptor Ligands

Benzodiazepine receptors are closely linked to the GABA receptor and are located on the same receptor complex. ¹¹C-Flumazenil (FMZ), an antagonist of the central benzodiazepine receptors/GABA, is a PET tracer, which demonstrates the distribution of benzodiazepine receptors in the brain. A role for this tracer may be in patients with TLE and normal MRI. In a combined analysis of 45 patients suffering from TLE⁶⁹ ¹¹C-FMZ PET showed decreased benzodiazepine receptor density in 38 patients, but only half of them were considered for surgery. In a group of studies totalling 102 patients with MRI negative extratemporal epilepsy,⁶⁹ 71 patients demonstrated an abnormality but only in a quarter of these was the abnormality contributory to the surgical decision. Despite these findings, FMZ PET may be useful in patients with TLE in whom FDG-PET scans shows a subtle or no abnormality, in patients with bilateral hypometabolism on FDG-PET, and in those patients undergoing evaluation after failed surgery. In some patients the ¹¹C-FMZ scan shows tracer uptake in the white matter and this may represent microdysgenesis.¹²⁸

Tracers binding to serotonin, opiate, and histamine receptors are being actively studied at present and may play an important role in the future.⁶⁹ A possible role for opiate receptors emerges from studies showing involvement of the opiate neurotransmission in postictal events. ¹¹C-carfentanil has a high affinity for *mu* opiate receptors. Studies in patients with TLE have shown increased binding in the temporal neocortex ipsilateral to the focus. Increase binding to the *mu* receptors points toward an increased inhibitory activity in

the temporal lobe and tonic inhibition of the epileptogenic activity.

Animal models of epilepsy have shown increased epileptogenesis with a reduced concentration of serotonin in the brain. However, increased serotonergic neurotransmission has been shown to have an anticonvulsant effect. ^{11}C -AMT has been tested in children with partial epilepsy and especially in children with TS. Epileptogenic tubers are associated with increased uptake affinity of this tracer in the interictal phase.

Secondary Epileptic Foci

A secondary epileptic focus is a site different from the primary focus and is located along the path or network of seizure propagation. Such foci may be dependent or independent from the primary focus. A dependent focus disappears after removal of the primary focus, but the independent focus may take up the role of primary focus by emerging as a new epileptic focus. This may be important in patients with long standing epilepsy, as there is ample opportunity for secondary epileptogenesis to develop.

A study by Savic and coworkers¹²⁹ showed that some of the abnormalities on ^{11}C -FMZ PET outside the primary focus are reversible after surgical removal of the primary focus. Juhasz and coworkers¹³⁰ reported a similar observation from their study with ^{11}C -FMZ PET; the authors conclude that such cortical areas of decreased tracer uptake, remote from the primary focus, are likely to represent the secondary epileptogenic foci. Similar results have been seen in patients with nonlesional epilepsy. This is important in surgical planning as these secondary foci may become epileptogenic after the removal of primary focus and result in poor outcome.

Conclusion: The Role of PET and SPECT in the Presurgical Evaluation of Children With Epilepsy

Both ictal SPECT and interictal PET provide useful information in temporal and extratemporal lobe epilepsy, but their role is more important in patients with normal structural imaging. Unfortunately, in these patients the sensitivity of either study is lowest in children with normal structural imaging. In TLE, a positive FDG-PET scan can show the epileptogenic focus in up to 85% of cases, whereas an ictal SPECT has a sensitivity between 80% and 90%. The sensitivity of ictal SPECT and interictal FDG-PET study in extratemporal epilepsy is around 50% to 60%. Although the sensitivity of nuclear medicine tests is greatest in cases of TLE, the clinical utility of the same tests is greatest in children with extratemporal epilepsy and nonlesional epilepsy. FDG-PET and ictal SPECT need complementary information from other noninvasive tests for accurate localization of the epileptogenic focus before proceeding to surgery. This means that EEG recording and/or MRI in TLE should localize to the same area. In case the information provided by other tests is discordant with the nuclear medicine tests or nuclear medicine is inconclusive then invasive EEG monitoring is necessary for accurate localization of the seizure focus.

Concordance between scalp EEG and structural imaging predicts the resectability of the lesion. However, in cases of cortical dysplasia, the visible lesion on MRI may underestimate the actual lesion that can be demonstrated by FDG-PET and/or ictal SPECT. The isotope study can show a wider area of hypometabolism and / or hyperperfusion and guide the placement of invasive EEG recording, thus aiding the neurosurgeon to achieve complete resection of the epileptogenic focus.

In patients with DNET and malformation of cortical development clearly seen on MRI, the use of nuclear medicine can provide valuable additional information. In a proportion of cases, ictal SPECT and FDG-PET scan may show a wider abnormality compatible with adjacent cortical dysplasia invisible on MRI; a wider resection of the lesion including this area of cortical dysplasia is associated with an excellent outcome. In the group of patients with cryptogenic infantile spasms 20 to 25% of cryptogenic cases can be re-classified as symptomatic by FDG-PET and are ideal candidates for surgery. Thus, FDG-PET and ictal SPECT add significant valuable information to the presurgical evaluation of children with drug resistant epilepsy and in experienced hands their routine use in an epilepsy surgical program is justified.

Brain Tumors in Childhood

Central nervous system (CNS) tumors are the most common solid tumors in childhood, accounting for 20% to 25% of all cancers. Although the prognosis has improved considerably during the last 2 decades, the overall cure rate today is approximately 60%, with the best prognosis for benign astrocytoma localized to the cerebellum (almost 100%) and the worst for brain stem gliomas (5-10%).¹³¹ Brain tumors are the leading cause of cancer mortality in children.¹³²

Descriptive classification by histological examination is crucial for the appropriate management of CNS tumors. Theoretically, all types of brain tumors might develop in children. However, the number of tumor types of special importance in childhood is significantly lower than in adults and is dominated by medulloblastoma, pilocytic astrocytoma, diffuse astrocytoma, ependymoma, and craniopharyngioma.¹³³

The treatment of children with CNS tumors is complicated and diverse, because the biologic behavior and management depends not only on the histological character of the tumor but also on location within the nervous system. The treatment of these children requires a multidisciplinary collaboration, including advanced diagnostic imaging, neurosurgery, chemotherapy, and radiotherapy, where surgical intervention is the mainstay of the diagnostic and therapeutic management of primary brain tumors. Surgical intervention is used to establish a histological diagnosis, to excise the tumor, or reduce its volume. Tumors localized centrally can rarely be totally resected without severe neurological deficits and even biopsies can be a major risk. Thus, the burden of late posttherapeutic effects is troublesome. Survivors of childhood CNS tumors often have severe neurological, neuro-cognitive and psychosocial sequelae¹³⁴⁻¹³⁸ due to either the tumor or its treatment.

Diagnostic imaging with CT and MRI (with MRI as first priority) generally is used to monitor the effect of treatment on tumor and recurrence, but image interpretation is impaired by changes in the brain tissue related to surgery, glucocorticosteroids, radiotherapy, and chemotherapy, leading to nontumor-related posttreatment contrast enhancement. Thus, because they add a functional dimension to brain scanning, other noninvasive diagnostic modalities, as PET, SPECT¹³⁹ and magnetic resonance spectroscopy¹⁴⁰ are suggested for grading and monitoring treatment effect and recurrence.

In general, the literature covering these topics in the pediatric field is relatively sparse and dominated by short communications, small patient series, and retrospective investigations, with the limitations and biases that follow. There are only a few studies available and most of them do not fulfil the requirements of high quality studies mostly due to the limited number of patients. In the following review, the limited published data concerning the use of radioisotopes in brain tumors in childhood are summarized.

The uptake and concentration of a radiolabeled compound in the tissue will depend on several factors. These include blood flow, determining how much tracer enters the organ, and the rate of transport from the blood to the brain tissue, which often will be limited by the BBB being impermeable to most hydrophilic substances. Furthermore, the volume of distribution and the possible binding to the tumor tissue, eg, metabolic trapping of FDG or binding of ligands to specific receptors, are also relevant factors. All these variables form a complex mosaic and it is not always obvious which mechanism is responsible for a high concentration of a radiotracer in a tumor. For diagnostic purposes it is important to have a high contrast between tumor and normal tissue and less important whether this is due to one or the other pathophysiological mechanism. However, a grasp of the basic pathophysiology is of utmost importance for our understanding of the nature of the diagnostic procedures and for guiding future developments.

Positron Emission Tomography

The tracers mainly used for brain tumor PET imaging in adults have been FDG, ¹¹C-methionine (MET)—and other radiolabeled amino acids—and ¹¹C-choline.

FDG-PET in Childhood Brain Tumors

FDG-PET is widely used for metabolic studies of brain tumors. The use of FDG-PET to grade tumor malignancy is based on the assumption that malignant tumors have a high FDG uptake and benign tumors have a reduced FDG uptake,¹⁴¹ compared with the average value of brain FDG uptake. FDG demonstrates enhanced uptake in the majority of malignant tumors, and the uptake is positively correlated with tumor malignancy in childhood CNS-tumors.¹⁴²⁻¹⁴⁵

The diagnostic value of FDG-PET previously has been investigated for grading of malignancy in adults.¹⁴⁶⁻¹⁵¹ These studies showed that the specificity for grading malignancy was not sufficient, as a great deal of overlap between high-grade and low-grade tumors existed; however, PET/MRI

coregistration with image fusion was shown to improve the accuracy in grading malignancy.^{152,153}

A limited number of PET studies in childhood CNS tumors have been published.^{142-145,150,154-160} Four small retrospective pre- and posttherapeutic studies^{144,145,158,159} and only 2 with a pretherapeutic prospective design^{142,143} report a potential clinical diagnostic value of FDG-PET. Four of these studies were focused on grading malignancy¹⁴²⁻¹⁴⁵ and found a correlation between FDG uptake and malignancy of tumor; however, there was significant overlap between different grades of malignancy. One of these studies systematically coregistered FDG-PET with MRI and showed an improved diagnostic value of FDG-PET in grading malignancy.¹⁴² However, the remaining problem to be solved is still the hypermetabolic benign tumors.¹⁵⁷

FDG-PET also has been proposed as a tool to improve the quality of brain tumor biopsies in adults¹⁶¹ and in children.¹⁵⁶ Although the delineation of tumor in the cerebral cortex is difficult, FDG-PET can be helpful in showing the part of the tumor which is most metabolically active; this feature can help direct biopsy.

FDG-PET has been used to further investigate areas of post-treatment contrast enhancement on MRI and differentiate benign changes from recurrent tumor.¹⁶²⁻¹⁶⁶ Some studies in adults report a high accuracy,^{162,164,167-169} whereas others show that PET is neither sensitive nor specific enough to be used routinely.^{170,171} Furthermore, FDG-PET has been used to describe the metabolic effect of various therapies on brain tumor metabolism^{141,172-175} in adults; a number of small clinical trials in adults have shown that changes in FDG uptake evaluated quantitatively may provide an early and sensitive dynamic marker of the effect of chemo- and radiotherapy.¹⁷² Only a few studies have investigated the possible value of FDG-PET in the diagnosis and follow-up of recurrent brain tumors in childhood. Plowman and coworkers¹⁵⁹ found FDG-PET useful in differentiating active tumor from post-treatment sequelae in 10 young patients with different brain tumors. In a study from Holthoff and coworkers,¹⁴⁵ including 15 children and young adults (0.5-26.0 years of age) with histologically confirmed brain tumors, FDG-PET was found to be a useful tool to evaluate metabolic activity of brain tumors over time and to assess response to treatment. Borgwardt and coworkers found FDG-PET with MRI coregistration useful in the monitoring of hypermetabolic childhood brain tumors.¹⁷⁶

A Brief Overview of Methods to (Semi-) Quantify FDG Uptake

FDG-PET has been used for a wide variety of indications in brain tumor imaging. The FDG uptake in tumors is dependent on different factors, for example, age, blood glucose, dose-injected versus weight and body consumption. In trying to compensate for these individual variations, different ratios and correction factors have been developed. Absolute metabolic rates of brain tumors were calculated initially, but this complex and time-consuming approach was replaced later by simple qualitative or semiquantitative analysis in the clinical routine.¹⁴⁷ Qualitative evaluation is achieved by visual analysis of PET images alone, using static

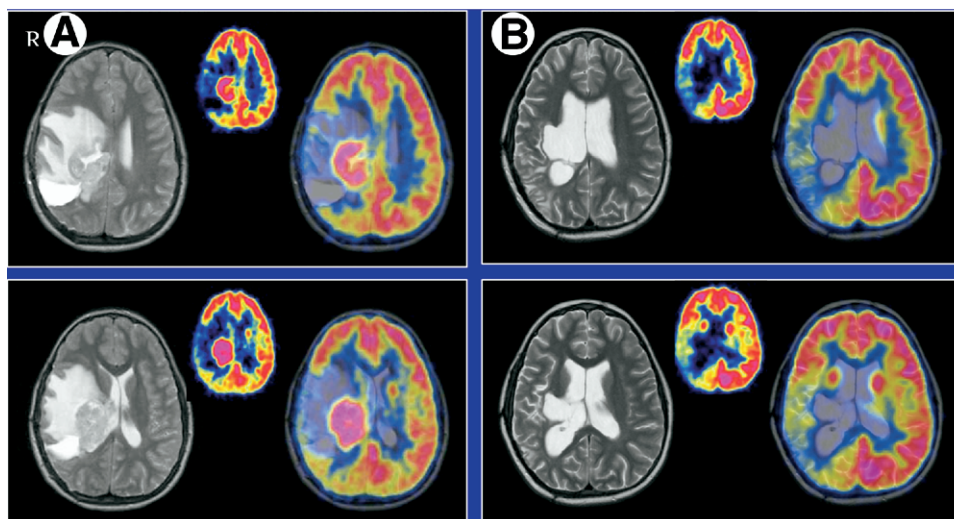


Figure 5 An 11-year-old boy was an anaplastic ganglioglioma in the right frontal region close to the lateral ventricle. (A) FDG-PET scan with MRI co-registration (T2) at diagnosis (after biopsy) and (B) FDG-PET with MRI co-registration (T2) at follow-up when a recurrence was suspected. The T2-weighted MRI scan at follow-up (B) shows contrast enhancement in the lateral posterior periphery of the surgical cavity, but the FDG-PET scan with MRI co-registration (B) shows no signs of local recurrence. The boy was disease free at 2-year follow-up. (PET and MRI images courtesy of Dr. Lise Borgwardt, Rigshospitalet, Copenhagen, Denmark.)

imaging without blood sampling. Semiquantitative measurements include calculation of the SUV, that is, normalizing FDG uptake to patient weight and injected dose. The SUV is defined as the radioactivity in tissue per milliliter divided by the injected dose multiplied by a patient-specific parameter (eg, body weight, body surface, lean body mass or body surface of lean body mass).¹⁵⁷ This involves easy computation, but is dependent on uptake time and glucose levels. Kinetic analysis is truly quantitative, but requires measurement of the arterial input function and mathematical modeling, making the procedure more invasive and the computation more complex.¹⁷⁷⁻¹⁸⁰

Currently, there is no consensus on the optimal scheme for brain tumor evaluation with FDG-PET. Determination of metabolic activity ratios, that is the ratio of the activity within the tumor to various “normal” structures, such as contralateral white matter or cortex, the basal ganglia, the cerebellum or even the whole brain, have been proposed as a means of assessing tumor uptake of FDG.^{143,147,181,182} SUV and SUV-to-normal brain ratios were not found useful in malignancy grading of childhood brain tumors.¹⁴³ The tumor/whole brain-ratio was also used in adults,¹⁸¹ but this method includes the diseased part of the brain both in the nominator and the denominator of the ratio, which leads to a systematic error, especially in large tumors. None of these ratios utilizes information from both white matter and gray matter in only nonaffected tissue, which is the basis of the tumor hotspot/brain-index.¹⁴²

Monitoring Therapy With FDG-PET To be able to differentiate early flare from recurrent tumor, the time between treatment and FDG-PET imaging is important with regard to data interpretation. No pediatric studies are available on this and the following reports are based on adult experi-

ences. For instance, surgery and radiotherapy may cause an acute inflammatory response, caused by activated macrophages and neutrophils¹³² and this may confound signal interpretation. Acute changes in relation to chemotherapy have also been reported. Tumor FDG uptake was increased in high grade gliomas when PET studies were performed within 24 hour of chemotherapy administration.¹⁷⁴ This appears to be a transient phenomenon since studies performed 7 to 14 days after initiation of chemotherapy showed a reduction in tumor FDG uptake in responding tumors.^{183,184} This early flare phenomenon may have prognostic significance as a measure of clinical and subclinical response to chemotherapy, but remains to be determined. The EORTC recommendation on when to perform a FDG-PET scan is within a period of 1 to 2 weeks after the end of chemotherapy.¹³² Examples of the use of FDG-PET in conjunction with MRI in the follow up of brain tumors are shown in Figures 5 and 6.

¹¹C-Methionine (MET) PET and Other Aminotracers

The physiological FDG uptake in normal gray matter makes interpretation of FDG-PET brain tumor studies difficult. Therefore, other tracers with greater tumor to background ratio, such as radiolabeled amino acids, have been proposed as an alternative in preoperative grading of malignancy. It seems, however, that the amino acids are more useful to differentiate between low-grade tumors and nonneoplastic lesions than for tumor grading.^{143,160,185}

¹¹C-methionine (MET) PET provides additional information in terms of delineation of tumor extent for local management of pediatric brain tumors.^{143,186} Recently, O-(2-[¹⁸F]fluoroethyl)-L-tyrosine PET has been found useful for biopsy-guidance in adults.¹⁸⁷ No pediatric publications concerning this issue are yet available.

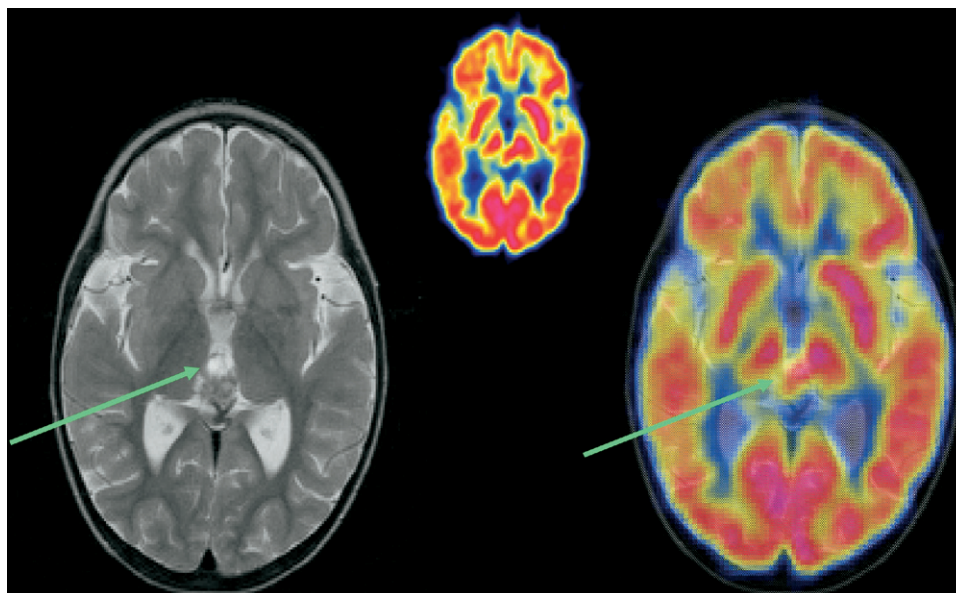


Figure 6 The MRI scan shows an area of contrast enhancement after chemotherapy, FDG-PET was used to differentiate residual tumor mass and treatment related contrast enhancement. The FDG-PET scan shows a focal area of viable tumor and the child was treated with radiation therapy. (PET and MRI images courtesy of Dr. Lise Borgwardt, Rigshospitalet, Copenhagen, Denmark.)

MET PET was found useful for further evaluation of post-treatment contrast enhancement on MRI in childhood CNS tumors in general.^{143,160} However, this tracer has a considerable nonprotein metabolism, because a significant fraction seems to be incorporated into phospholipids through the S-adenyl-methionine pathway, which generates a substantial amount of nonprotein metabolites and makes quantification of protein synthesis difficult.¹⁸⁸ Other amino acids, such as ¹¹C-tyrosine and ¹¹C-leucine, have been proposed as better protein synthesis rate imaging agents, but the clinical experience with these radiotracers is still limited. ¹¹Carbon labeling is also a limiting factor for routine clinical use and for regional distribution, because of the short half-life. Tyrosine can also be labeled with ¹⁸F with high yield and specific activity. ¹⁸F-tyrosine appears promising to replace MET and complement FDG in brain tumor diagnosis.

¹¹C-Choline

Recent studies have shown the potential usefulness of ¹¹C-choline in brain tumors^{189,190}; it may be promising in discriminating between benign and malignant brain tumors,¹⁹¹ although other studies report of similar difficulties with overlap between high- and low-grade tumors. Choline analogs are phospholipid precursors and have been shown by magnetic resonance spectroscopy to be present in increased concentrations in brain tumors, particularly high-grade lesions, probably representing the activation of choline uptake and phosphorylation in tumor cells. Choline metabolism in tumor cells is directed primarily toward membrane synthesis, and de novo synthesis of choline is negligible in tumor cells as the cell membrane is duplicated at the same rate as the rate of cell duplication.

The recently developed ¹⁸F-choline is believed to be superior to ¹¹C-labeled choline because of the longer half-life and

the shorter positron range,¹⁹² making synthesis of the compound and handling of the patient much easier. No pediatric studies are available yet.

Other Tracers

Recent studies have addressed tumor proliferation imaging with radiolabeled nucleoside analogs; these tracers measure DNA-synthesis and thereby can estimate tumor-cell proliferation. These studies constitute an attempt to provide a non-invasive measurement of tumor growth potential and therefore to evaluate the grade of malignancy, and to identify the most rapidly proliferating regions of the tumor. The radiolabeled nucleoside analogs [18F]-3'-fluoro-thymidine¹⁹³ and the [2'-deoxy-2'-[¹⁸F]fluoro-beta-D-arabinofuranosyl nucleosides¹⁹⁴ seem promising, but reports on the use of these tracers in human brain tumor imaging have not been published yet.

PET using the tracer H₂¹⁵O has been used to study cerebral blood flow (CBF). Blood flow has been found to be depressed in adult gliomas, where the most malignant gliomas tend to have the largest reduction in regional CBF (rCBF).¹⁷³ PET with H₂¹⁵O showed no correlation to the grade of the brain tumor in childhood CNS-tumor.¹⁴²

Most of the interest in PET lies in the labeling of specific molecules such as drugs. An example is ¹¹C-temozolamide, whose different uptake in brain tumors and normal brain can be determined over time by regional tracer kinetics.¹⁹⁵ No pediatric studies are available yet.

The Clinical Value of PET

The published studies suggest that PET is an important supplement in the diagnostic workup, primarily in differentiating recurrences from treatment-related contrast-enhancement, but also in the areas of monitoring therapy, biopsy

guidance and treatment planning. The studies suggest a combination of FDG and amino acid tracer to get the optimal delineation of tumor, the area of the highest metabolism and the ability to differentiate nonneoplasm from low-malignant neoplasm. In this case, a pretherapy FDG-PET scan is recommended in order to access the metabolic nature of the tumor at diagnosis and to obtain a baseline study, useful for comparison with follow-up FDG-PET scans.

To use FDG-PET in pretherapeutic malignancy grading, knowledge of the imaging qualities of the FDG-PET hypermetabolic benign tumors needs to be further developed, though FDG-PET has a high predictive value in brain tumor grading, compared with other PET and SPECT tracers.

Furthermore, published studies show that it is necessary to define the anatomy of the tumor; this is why MRI coregistration has to be part of the clinical routine. Each imaging technique has its own strengths and limitations, and to make full advantage of the different and often complementary information they provide one needs to combine them. Several methods for image registration and fusion are now available in many commercial systems. Although PET/CT scanners are widely used for brain imaging, co-registration of functional images with CT is not the same as co-registration of the same images with MRI.

Although PET has a high resolution compared with SPECT, with a greater variety of more specific PET tracers for brain tumor imaging and a higher resolution in the new PET brain scanners, it is likely that the role of PET in the management of childhood brain tumors will expand further.

Single-Photon Emission Computed Tomography

SPECT generally has a poorer resolution than PET, but its use has expanded resulting from the number of tracers available developed throughout the last 2 decades. The tracers mainly used for brain tumor SPECT imaging in adults are ^{201}Tl thallium (Tl), $^{99\text{m}}\text{Tc}$ -sestamibi (methoxyisobutylisonitrile or MIBI), $^{99\text{m}}\text{Tc}$ -tetrafosmin (TF; TF will not be further mentioned, because there are no pediatric publications available), ^{123}I -alpha-methyl-tyrosine (IMT), and ^{111}In pentetreotide. Most of the pediatric publications are on Tl.¹⁹⁶⁻²⁰²

^{201}Tl Thallium

^{201}Tl is a monovalent cationic radionuclide with a chemical behavior similar to potassium as it crosses the cell membrane via the sodium-potassium ATPase pump. Unlike potassium that binds only to 1 site, ^{201}Tl has 2 binding sites on the enzyme system and this may explain its prolonged clearance from the cell. Uptake requires cell viability and has been shown to be greater in tumor cells than in normal connective tissue or inflammatory cells, and it is negligible in areas of necrosis.²⁰³ In a comparative study with pathological correlation, the mechanism of ^{201}Tl accumulation in primary brain tumors was thought to be a function of blood flow and tissue viability, with alterations in the blood brain barrier also playing a role.²⁰⁴

Thallium SPECT has been established as a potentially useful tool for the assessment of brain tumors. In adults with

gliomas, SPECT using ^{201}Tl has been used to predict the histological grade,^{205,206} to improve delineation of the area of active tumor, and to help differentiate between residual tumor and radiation necrosis.²⁰⁵⁻²⁰⁷ Although some studies have suggested a similar usefulness for thallium SPECT in childhood brain tumors,^{196,197,199-202} other prospective studies have failed to demonstrate any clinical advantage over MRI.¹⁹⁸ Maria and coworkers demonstrated thallium to be a specific marker for neoplastic disease in the brain, though there was no correlation between thallium uptake and histological grade of brain tumors.¹⁹⁹ A high sensitivity and specificity of thallium SPECT for detection of childhood brain tumors, found by O'Tuama and coworkers, confirmed these findings.^{196,202} Thallium SPECT uptake in brainstem gliomas was correlated to clinical progression, although MRI with gadolinium seemed more sensitive in detecting early recurrence. In this group of tumors, it was difficult to prove an advantage of thallium SPECT over gadolinium MRI.²⁰⁰ In a comparison of thallium SPECT and FDG-SPECT in childhood brain tumors, Maria and coworkers¹⁹⁷ found that thallium SPECT could be interpreted in 18 of 19 patients without MRI confirmation, whereas none of the 19 FDG-SPECT studies could be interpreted without MRI to localize tumor delineation. The authors concluded that thallium SPECT seems to be the most promising imaging modality in this area, primarily in tumor recurrence, when MRI is equivocal and further, radiation necrosis does not accumulate thallium. The advantages of thallium SPECT are mainly explained because of greater tumor to background ratio. O'Tuama and coworkers found thallium SPECT to be correlated to disease outcome.²⁰¹ No pattern for HMPAO uptake was observed in childhood brain tumor in the combined studies.^{199,202}

$^{99\text{m}}\text{Tc}$ Sestamibi

$^{99\text{m}}\text{Tc}$ -methoxyisobutylisonitrile (MIBI), or sestamibi, has been suggested to offer advantages over thallium for imaging of brain tumors in adults.²⁰⁸ This molecule does not penetrate the intact BBB and is taken up by normal choroid plexus, pituitary, scalp, and nasopharyngeal tissues.¹⁹⁶ In particular, MIBI enters the cells through a passive pathway and accumulates in the mitochondria mainly according to the mitochondrial and plasma membrane potentials. It was originally introduced for myocardial perfusion studies and thereafter proposed as tumor-seeking agent.²⁰⁹ Adult brain malignancies such as astrocytoma, accumulate $^{99\text{m}}\text{Tc}$ -MIBI²⁰⁹; $^{99\text{m}}\text{Tc}$ -MIBI SPECT can add valuable information to CT for the differentiation of radiation necrosis from recurrent disease.²¹⁰

$^{99\text{m}}\text{Tc}$ -MIBI uptake by viable tumor cells and brain malignancies in childhood has been studied as well.^{196,211,212} In the first series reporting the use of MIBI in brain tumors imaging, 19 children also were studied with ^{201}Tl SPECT and CT/MRI.¹⁹⁶ Both radiotracers showed negligible uptake in normal brain, reflecting almost a total exclusion by the BBB; the most important difference was the strong and selective MIBI uptake by the choroids plexus. This uptake is specific and independent of the pertechnetate carrier because it occurred despite pretreatment with potassium perchlorate, which is

able to inhibit pertechnetate uptake by the choroids plexus. The distribution of both tracers in the tumor was similar, with a sharper definition of the lesion boundary by MIBI, probably attributable to the better physical properties of ^{99m}Tc , an interesting advantage for the possible applications in stereotactic radiosurgery. Nevertheless, the physiologic MIBI uptake by the choroids plexus is a disadvantage for the evaluation of lesions lying close to the ventricle in the deep paraventricular regions. Furthermore the authors stated that fusion imaging would increase the value of the complementary information obtained by SPECT and CT/MRI in isolation in defining of the area of active tumor, in particular for the precise identification of its true limits, especially in patients studied after treatment.

Despite the potential advantages and some experience with ^{99m}Tc -MIBI SPECT in children, a clear advantage over other modalities, including ^{201}Tl SPECT, in imaging brain tumors has not been established,^{196,211,212} despite the already mentioned clearer definition of tumor boundaries using MIBI.

^{123}I -Alpha-Methyl-Tyrosine

IMT is a synthetic amino acid analog taken up by brain tumors, in particular gliomas, with minimal uptake in the normal brain; this is why IMT SPECT can be used to image brain tumors. This tracer uses a carrier system to cross the BBB but is not incorporated in proteins. In adults, IMT SPECT has shown ability to visualize intracranial tumors with satisfactory tumor to background ratio; moreover, it accurately differentiates viable tumor tissue from scar and necrosis.²¹³ In a comparative study IMT SPECT was found to be as accurate as ^{11}C -MET PET in brain tumor imaging.^{214,215} When used in combination with ^{201}Tl SPECT, it is more accurate than either itself as a standalone technique or ^{11}C -MET PET in the differential diagnosis of brain space occupying lesions.⁸⁰ However, the more interesting clinical applications of IMT are in radiation therapy planning, with SPECT/CT fusion imaging playing an essential role.

IMT SPECT also has been used to monitor tumor activity in low-grade gliomas of childhood. In a very small retrospective comparative trial with a broad histological profile of low-grade gliomas and no SPECT/CT image-fusion Molenkamp and coworkers¹⁵⁴ found ^{123}I -alpha-methyltyrosine SPECT to be superior to CT, MRI and FDG-PET in tumor activity monitoring in a small retrospective study.

^{111}In -Pentetreotide

Somatostatin is a naturally occurring neuropeptide that inhibits cellular proliferation and differentiation.²¹⁶ ^{111}In -pentetreotide scintigraphy is a well-established method used to evaluate patients with neuroendocrine tumors.²¹⁷ Although a good correlation between scintigraphic findings and in vitro somatostatin receptor density has been reported in many peripheral tumors, the situation is different in the central nervous system.²¹⁸

Medulloblastoma, the most frequent brain tumor in children, shows a high expression of type 2 somatostatin receptors; a previous study in 20 children demonstrated the use-

fulness of somatostatin receptor scintigraphy to detect medulloblastoma recurrence in treated patients.²¹⁹

Clinical Value of SPECT

SPECT imaging in childhood brain tumors with several different tracers still plays a useful clinical role in the diagnostic workup, mainly because of its availability, despite the growing use of PET. With the new SPECT/CT fusion scanners the sensitivity and specificity is likely to improve, because the relatively poor spatial resolution and the low signal-to-noise ratio will be less important with a better anatomical localization; MRI, however, is a better diagnostic tool for coregistration in brain tumor imaging.

Clinical Value of Radioisotope Imaging in Childhood Brain Tumors

The ongoing technological improvements will keep SPECT and PET examinations in childhood brain tumor imaging evolving and expanding. Their clinical value is likely to increase, with a role in the diagnostic workup as well as histological grading, biopsy guidance, treatment planning, and follow-up of brain tumors in childhood. Fusion of functional imaging with anatomical imaging together with synthesis of new tracers is likely to be the most important developing areas.

Other Indications of Nuclear Medicine in Pediatric Neurology

The maturational changes in brain glucose metabolism as detected by functional imaging were described by Chugani and coworkers.²²⁰ FDG-PET studies in term newborns with hypoxic-ischemic encephalopathy have shown that, during the subacute period after the peri-natal asphyxia, cerebral glucose metabolism correlates well with the severity of encephalopathy and with the short-term clinical outcome.^{221,222} SPECT also has been used in studying perinatal asphyxia.²²³

Muller and coworkers²²⁴ studied brain organization for language in children, adolescents, and adults with left hemispheric lesions. They found enhanced postlesional plasticity of the brain in childhood. A summary of functional imaging of neuropsychiatric disorders in childhood was published by O'Tuama and coworkers.²²⁵ The focus has primarily been on attention deficit hyperactivity disorder,^{226,227} anorexia nervosa,²²⁸ bulimia nervosa,²²⁹ and obsessive-compulsive disorder.²³⁰

Different types of inflammatory neurological diseases in infants have been investigated using FDG-PET; Rasmussen's encephalitis^{231,232} and use of FDG-PET in HIV-1 infected children born to seropositive mothers.²³³ PET and SPECT have also been used to study the pathophysiology of many other childhood brain disorders such as Rett syndrome,^{234,235} neurofibromatosis,²³⁶ sickle cell encephalopathy,^{237,238} and traumatic brain injury.²³⁹

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