NEUROIMAGING IN EPILEPSY

Craig Watson, MD, PhD, Gregory J. Moore, PhD and Harry T. Chugani, MD

BACKGROUND– In the past 10 to 15 years, the development of several types of high-resolution tomographic neuroimaging modalities has dramatically altered the diagnosis and management of patients with epilepsy.

REVIEW SUMMARY– In this review, we consider the impact, sensitivity, specificity, and prognostic implications of the newer structural and functional imaging modalities such as computed tomography scanning, magnetic resonance imaging (MRI), magnetic resonance spectroscopy, positron emission tomography, and single photon emission computed tomography. Recent advances such as quantitative MRI techniques and new positron emission tomography and single photon emission computed tomography probes are also discussed to alert the practicing neurologist to their impending emergence into the field of epilepsy neuroimaging.

CONCLUSIONS– The development of new MRI and functional neuroimaging modalities will continue to expand research opportunities, treatment options and practices, and insight into our basic understanding of the processes of epileptogenesis.

KEY WORDS *neuroimaging, epilepsy, CT, MRI, MRS, PET, SPECT*

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The advent of a variety of high-resolution tomographic neuroimaging modalities in the past 10 to 15 years has had a significant impact on the diagnosis and management of patients with epilepsy. Anatomical or structural imaging with computed tomography (CT) scanning and magnetic resonance imaging (MRI) can readily detect anatomical abnormalities and structural lesions associated with seizures in the patient with epilepsy. Recent development of quantitative techniques has expanded the sensitivity and scope of structural imaging to the point where we are able to detect and quantify epileptogenic lesions previously detected only by pathological examination of surgical specimens or at autopsy. Magnetic resonance spectroscopy (MRS) imaging can demonstrate changes in the chemistry of epileptogenic brain tissue, both in the interictal state and immediately after a seizure.

Because epilepsy is primarily a functional disturbance of the brain, functional neuroimaging modalities, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), are also very sensitive in detecting generalized and focal abnormalities in patients with epilepsy. New probes for functional imaging in the epilepsies are being developed at a rapid pace and will provide important insight into the biochemistry and neuronal circuitry of seizures.

From the Departments of Neurology (C.W., H.T.C.), Anatomy (C.W.), Psychiatry and Behavioral Neurosciences (G.J.M.), Radiology (G.J.M., H.T.C.), and Pediatrics (H.T.C.), Wayne State University School of Medicine, Detroit, Michigan, and Children's Hospital of Michigan, Detroit (H.T.C.).

Send reprint requests to: Craig Watson, MD, PhD, WSU/DMC Comprehensive Epilepsy Program, Department of Neurology, WSU School of Medicine, 6E-UHC, 4201 St. Antoine, Detroit, MI 48201.

SKULL X-RAY

In general, skull x-rays are of limited value in evaluating the patient with epilepsy. In the setting of acute head trauma,

skull x-rays may be useful in diagnosing fractures associated with brain injury and seizures.

The other main utility of skull x-rays is in the demonstration of intracranial calcification, although they do not do so nearly as well as CT scanning. For this reason, skull x-rays rarely are used in the evaluation of patients with epilepsy except in developing countries where CT scanning may not be available. In that setting, however, the two most common diseases associated with intracranial calcification and epilepsy are tuberous sclerosis and Sturge-Weber syndrome. The skull x-ray in tuberous sclerosis may show calcification along the walls of the ventricles as well as in cortical tubers. In Sturge-Weber syndrome, the diagnosis may be made by skull x-ray when it demonstrates the classic "tram track calcifications," which outline the convolutions of the parieto-occipital cortex. Cerebral angiography in patients with Sturge-Weber syndrome reveals the presence of arterial thrombosis, the absence of cortical veins, aberrant cerebral venous drainage, and arteriovenous malformations in addition to the characteristic leptomeningial angioma commonly located in the parieto-occipital region (1,2).

COMPUTED TOMOGRAPHY SCANNING

The development of CT scanning in the mid 1970s represented a significant advance over nuclear brain scans and skull x-rays in the evaluation of patients with epilepsy. For the first time, it was possible to directly visualize the brain in vivo and to detect a variety of pathologic entities causing epilepsy that were previously detected only at postmortem examination. In an early CT study, it was discovered that approximately half of a large epileptic population showed some abnormality on CT scan, although these findings were often nonspecific atrophic changes (3).

As with skull x-rays, CT scanning has proven especially advantageous in the setting of intracranial calcification, skull fracture, and diseases resulting in acute bleeding into or around the brain. Therefore, CT scanning may be especially useful in posttraumatic seizures (4), Sturge-Weber syndrome, and conditions resulting from developmental anomalies of the brain such as hemimegalencephaly, gross malformations of the brain, and tuberous sclerosis.

Magnetic resonance imaging scanning is now the imaging study of choice in the initial evaluation of patients with epilepsy.

However, the yield of surgically treatable lesions detected by CT scanning has been disappointingly low. Aside from intracranial tumors and vascular malformations, only a small percentage of lesions detected by CT scan have been amenable to surgical treatment (5,6).

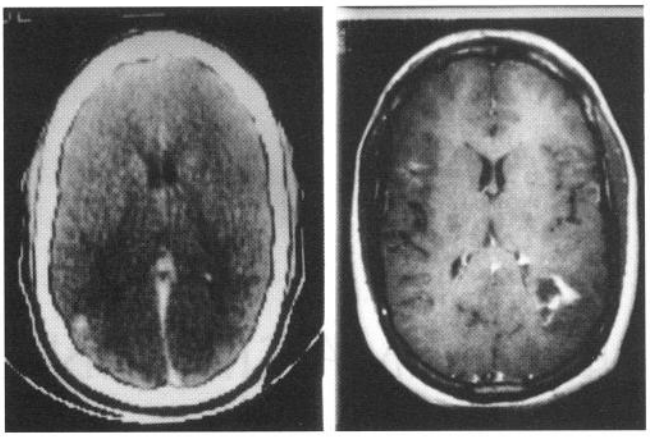

Figure 1.
Horizontal (axial) CT scan (left) and gadolinium-enhanced T1-weighted MRI scan (right) from a patient with right-sided sensory simple partial seizures showing the clear superiority of MRI over CT in detecting this left-sided low- to medium-grade astrocytoma.

The most common pathological finding in patients with medically intractable temporal lobe epilepsy is hippocampal sclerosis. Approximately 60 to 75% of patients with temporal obe epilepsy undergoing surgical treatment are discovered to have this pathologic entity. It is characterized by neuronal loss and gliosis affecting sectors CA1, CA3, and CA4 of the hippocampus with sparing of CA2, the subiculum, and the dentate gyrus, although occasionally there is more widespread pathology in severe cases. Because this is a common pathologic finding in medically intractable temporal lobe epilepsy, attempts were made to detect hippocampal sclerosis with CT scanning before surgery (7,8). In general, the success of CT scanning in detecting hippocampal sclerosis was extremely poor due to its lack of high spatial resolution and poor contrast between gray matter and white matter structures.

MAGNETIC RESONANCE IMAGING

Qualitative Imaging

Small Structural Lesions – MRI scanning is now the imaging study of choice in the initial evaluation of patients with epilepsy. Since the development of MRI in the mid 1980s, small and subtle structural lesions not previously detected with CT scanning can now be detected. These lesions include small areas of increased gliosis or sclerosis, tumors, vascular lesions, vascular malformations, focal atrophy, and malformations of brain development including a number of small and sometimes localized abnormalities known as neuronal migration disorders. Several studies have shown MRI to be superior to CT scanning in the detection of tumors, vascular malformations, infections, and other small lesions—

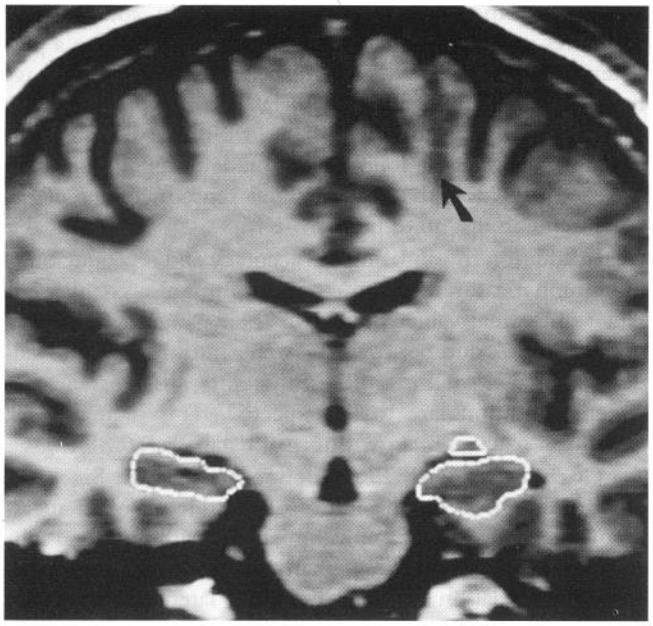

Figure 2.
Coronal MRI scan showing an area of left frontal heterotopia (arrow) and normal and symmetric hippocampal volumes (outlined bilaterally). The patient had simple partial and complex partial seizures beginning in the left frontal lobe.

including those arising from the medial temporal lobe region —causing partial seizures in children and adults (9-45) (Fig. 1). Although gadolinium-enhanced MRI scans are useful in certain settings, the routine use of contrast enhancement is not necessary in the evaluation of patients with partial seizures (46).

Neuronal Migration Disorders – Even with the high spatial resolution and sensitivity of MRI, extremely small regions of disordered neuronal migration called microdysgenesis may not be detected. This entity has been reported in up to 43% of temporal lobe specimens (47). However, many small and subtle areas of disordered neuronal migration can be detected with MRI. As with tumors and vascular malformations, MRI is clearly superior to CT scanning in the detection of a variety of neuronal migration disorders that are often associated with epilepsy. These range from small areas of focal cortical dysplasia manifested by a thickening of the cerebral cortex on MRI scan, through small- to moderate-sized areas of abnormally located cortical neurons (heterotopias), to a large continuous band of heterotopic gray matter present between the cerebral cortex and the lateral ventricles known as a "band heterotopia" or "double cortex" (48-55) (Fig. 2).

Hippocampal Sclerosis – The success of qualitative MRI in detecting hippocampal sclerosis has varied widely in reported studies (12,15,17,18,21-23,27-29,31-34,56-59). The best results have been obtained using a combination of MRI criteria such as increased signal intensity on T2-weighted images, decreased signal on T1-weighted images, disruption of internal hippocampal structure, and hippocampal atrophy (60-68). When these criteria are applied to thin (3- to 5-mm), coronal magnetic resonance (MR) images obtained in a plane perpendicular to the long axis of the hippocampus, hippocampal sclerosis can be detected in 70 to 85% of cases.

Correlation with Outcome – Several studies have shown a correlation between abnormalities detected on MRI and outcome after surgical treatment in medically intractable temporal lobe epilepsy (69-75). The presence of a structural lesion or hippocampal atrophy on MRI scan is associated with a seizure-free outcome in 62 to 87% of cases in these studies. A normal MRI scan, on the other hand, is associated with a seizure-free outcome in only 21 to 56% of cases. Therefore, the presence of either hippocampal atrophy or a structural lesion is a strongly positive prognostic sign in patients undergoing temporal lobectomy for medically intractable temporal lobe epilepsy.

Quantitative Imaging

Volumetric Magnetic Resonance Imaging – The development of high-resolution neuroimaging techniques such as MRI-based volumetric measurements of the amygdala and hippocampus has been useful in obtaining in vivo neuroanatomic information in a number of clinical settings including temporal lobe epilepsy, amnestic patients, and Alzheimer's disease. Studies have shown that significantly reduced hippocampal volumes corroborate neurophysiologic studies and allow lateralization of the epileptogenic region, correlate with neuropathologic and neuropsychologic abnormalities, and correlate with outcome after temporal lobectomy. As experience and information accumulate, we expect that quantitative MRI techniques, as well as other neuroimaging studies, will reduce the number of patients who require invasive, prolonged, and expensive electroencephalogram (EEG) monitoring, thereby allowing more patients to be treated effectively using noninvasive EEG monitoring coupled with noninvasive imaging techniques and neuropsychological studies.

Quantitative MRI also allows the correlation of preoperative and postoperative amygdaloid and hippocampal volumes with neuropsychological, neuropathological, and clinical findings. The addition of amygdaloid volume measurements to hippocampal volume measurements may allow assessment of the relative contribution of each of these structures to epileptogenesis and memory function. Postoperative quantification of the amount of amygdaloid and hippocampal resection may yield a better understanding of which structures need to be removed and in what volume. Preliminary data suggest that amygdaloid and hippocampal volume measurements may also be helpful in providing supplementary information in patients with bilateral temporal ictal onset when used in conjunction with EEG monitoring, neuropsychological studies, intracarotid amobarbital testing, and functional neuroimaging studies.

Technical Aspects. In order to obtain accurate and reproducible results with MRI-based volumetric measurements of the hippocampus and amygdala, attention must be directed to a number of technical aspects. The first of these are the aspects of MR image acquisition and image processing. The details of these components of volumetric imaging are beyond the scope of this article but have been reviewed recently by Jack (76). Briefly, the procedure involved in MRI-based volumetric measurements of the hippocampus and amygdala is as follows. High-resolution, thin (1.5- to 3-mm), contiguous coronal images are obtained perpendicular to the long axis of the hippocampus. Most centers at this time use a three-dimensional coronal volumetric spoiled gradient echo sequence to obtain these images in a relatively brief imaging time. The images are then transferred to a computer workstation, and the contours of the hippocampus and amygdala are manually outlined sequentially on each slice from anterior to posterior. The computer calculates the volumes by counting the number of voxels outlined using a region of interest function. The number of voxels is then multiplied by the voxel volume to give a total volume of each structure in cubic millimeters. Many investigators then calculate a ratio for comparing the relative sizes of the left and right amygdala and left and right hippocampus. In our institution, we simply divide the volume of the smaller structure by the larger to obtain a measure of symmetry between the two sides. The absolute volumes of the two amygdalae and hippocampi are also obtained, and these absolute volumes and the ratios are compared with a normal control population. In the interpretation of the data, hippocampal or amygdaloid sclerosis is diagnosed if the absolute volumes are greater than 2 standard deviations smaller than the control population or if the ratios are less than 0.90.

Studies have shown that significantly reduced hippocampal volumes corroborate neurophysiologic studies and allow lateralization of the epileptogenic region, correlate with neuropathologic and neuropsychologic abnormalities, and correlate with outcome after temporal lobectomy.

In order to obtain accurate and reliable results with volumetric MRI measurements, the person measuring the volumes must have an intimate and detailed knowledge of the anatomy of the medial temporal region. In addition, the structures must be measured consistently according to a predetermined and standardized protocol. Such protocols have been published in detail (76-79). When the boundaries of the hippocampus and amygdala are measured by a knowledgeable investigator following a predetermined and standardized protocol, the accuracy and reproducibility of the measurements are quite high (76-84).

In addition to validating the accuracy and reproducibility of volume measurements, each center must also establish the range of normal values present in their patient and control populations. A number of factors enter into the absolute values obtained at each institution; therefore, discrepancies between institutions are to be expected. This requires each institution to create its own normal database (76-88).

Correlation with Electroencephalogram. Since the initial publication on the utility of volumetric MRI measurements of the hippocampus in patients with temporal lobe epilepsy by Jack et al (89), many studies have shown the positive correlation between the EEG lateralization of the epileptogenic region in temporal lobe epilepsy and the presence of significantly reduced hippocampal volumes (90-104). The sensitivity and specificity of these observations varies depending on the patient population studied, but all of the studies found the two techniques to be complementary and valuable. In a recent study, we found that volumetric studies of the hippocampus and amygdala were helpful in lateralizing the epileptogenic region as defined by extracranial and intracranial EEG. Hippocampal volumes were more sensitive than amygdaloid volumes and provided lateralization in 87% of cases. However, when both hippocampal and amygdaloid volumes were considered, lateralization was obtained in 93% of cases (101). Therefore, MRI-based volumetric measurements of the hippocampal formation and amygdala appear to be very sensitive in lateralizing the epileptogenic region.

Correlation with Pathology. Studies have been performed in which the MRI hippocampal volumes were correlated with pathologic analysis of specimens obtained at temporal lobectomy (105-112). In these studies, a strong relationship between the degree of hippocampal volume loss and the severity of hippocampal sclerosis was present (Fig. 3). These findings have been consistent in studies that used qualitative (105,107), semiquantitative (111,112), and quantitative (106,108-110) neuropathologic techniques. On the basis of these studies, it appears that the severity of hippocampal sclerosis can now be predicted preoperatively with the use of MRI-based hippocampal volumes and hippocampal ratios. This affords us a powerful tool in the clinical diagnosis and treatment of patients with hippocampal sclerosis and in research into this common cause of medically intractable temporal lobe epilepsy.

Correlation with Neuropsychological Studies. It is well-recognized that medial temporal lobe structures such as the hippocampus and amygdala play a critical role in declarative or representational memory function. The same medial temporal lobe structures are involved in other neu-

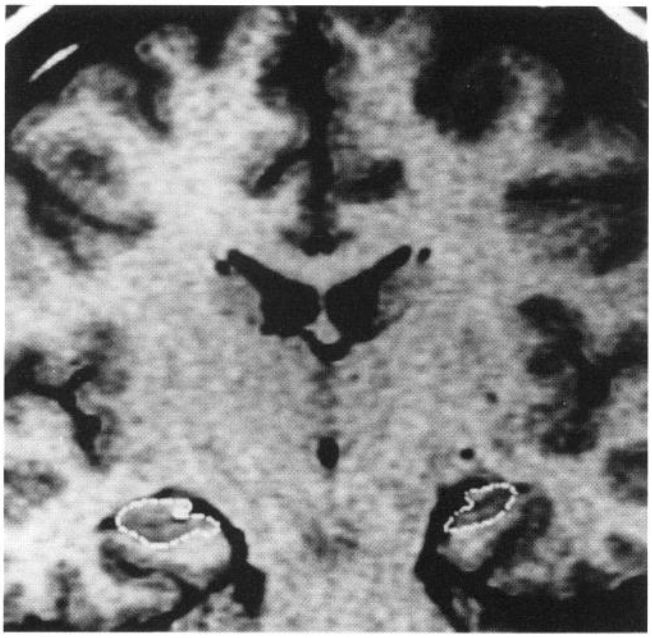

Figure 3.
Coronal MRI scan passing through the bodies of the hippocampi (outlined bilaterally) showing severe left hippocampal atrophy (ratio = 0.59). Severe hippocampal sclerosis was found on pathological examination.

rologic conditions resulting in memory deficits such as postanoxic amnesia and Alzheimer's disease. It is not surprising, therefore, that a relationship has been demonstrated between the severity of hippocampal atrophy, as measured by volumetric MRI studies, and memory function using a variety of neuropsychological test instruments (108,113-125). In general, a significant relationship between left hippocampal volume and verbal memory function has been found in a number of studies (108,113,117,118,120,121,124,125). An interesting finding is that patients undergoing left temporal lobectomy with severe left hippocampal atrophy have less verbal memory deficit postoperatively than those with lesser degrees of left hippocampal atrophy (117,118,120). A number of studies have shown a correlation between hippocampal atrophy, as demonstrated on volumetric MRI, and poor memory function on the intracarotid amobarbital test (119,122,123). Some studies have also shown a relationship between impaired nonverbal memory function and reduced right hippocampal volumes (116,121).

Correlation with Outcome After Temporal Lobectomy. A significant relationship has also been demonstrated between MRI-based hippocampal volumes and outcome after temporal lobectomy (126). In this study, if EEG lateralization was concordant with hippocampal atrophy, 97% of the patients had a favorable outcome (seizure free or nearly seizure free). However, if the hippocampal volumes were not lateralizing, the percentage of patients with a favorable outcome dropped to 42%, and if the hippocampal volumes were abnormal on the side opposite the side of surgery, only 33% of patients had a favorable outcome. Similar results have been found in patients requiring depth electrode recordings (127).

Clinical Correlations. Several studies have shown a significant relationship between MRI-based hippocampal and amygdaloid atrophy and a history of febrile convulsions in early childhood (128-134). These investigations found that hippocampal atrophy ipsilateral to the side of seizure onset is significantly more common in patients with a history of early childhood febrile convulsions. Whether the early febrile convulsion damages the hippocampus and is therefore a cause of hippocampal sclerosis remains quite controversial. Another possibility is that the child has a prolonged febrile convulsion because the hippocampus was previously damaged due to a prenatal or perinatal insult. As will be discussed later, the association of hippocampal sclerosis with other developmental anomalies such as cortical dysplasia and heterotopias may lend credence to the latter explanation.

A related question revolves around whether hippocampal sclerosis is the cause of repeated seizures or is a consequence of them. Investigations have shown that no significant relationship exists between MRI-determined atrophy and the duration and frequency of seizures (130,135-138). These studies, taken together with the febrile convulsion studies, seem to suggest that hippocampal sclerosis may be due to an insult early in life that remains relatively stable and that each complex partial seizure does not cause further neuronal cell loss or progressive worsening of hippocampal atrophy.

Another group of patients with a history of early childhood neurologic insult was described by Cascino et al (139,140). This group of 13 patients had a history of early childhood neurologic insult in the form of prolonged febrile convulsions or bacterial meningitis. All of them developed medically intractable complex partial seizures and were noted to have an upper motor neuron facial weakness and facial asymmetry contralateral to the side of seizure origin. This group of patients also exhibited significantly reduced hippocampal volumes, as determined by volumetric MRI, ipsilateral to the side of seizure onset. Hippocampal sclerosis was present in all of the surgically excised temporal lobes in this patient group, and 83% of the patients were seizure free after surgery.

Another interesting group of patients with medically intractable temporal lobe epilepsy, early childhood neurologic insult, and volumetric MRI changes was recently described by Cendes et al (141,142). They studied a series of 50 patients with intractable temporal lobe epilepsy and discovered that 34% of them had a clear history of fear accompanied by a rising epigastric sensation as the initial manifestation of their seizures. In this subgroup of patients, MRI-based volumes of the amygdala were significantly smaller than those of the remaining 66% of their study group. Postoperative pathologic examination verified the volumetric MRI findings. This group of patients with more pronounced amygdaloid atrophy more commonly had prolonged febrile con-

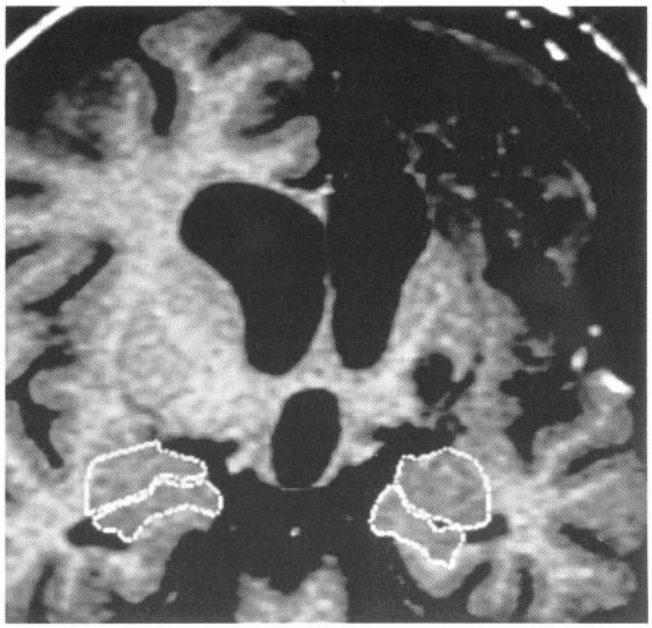

Figure 4.
Coronal MRI scan showing a large left frontal arteriovenous malformation and normal and symmetric hippocampal (lower outlines) and amygdaloid (upper outlines) volumes bilaterally. The patient experienced simple partial and complex partial seizures beginning in the left frontal lobe.

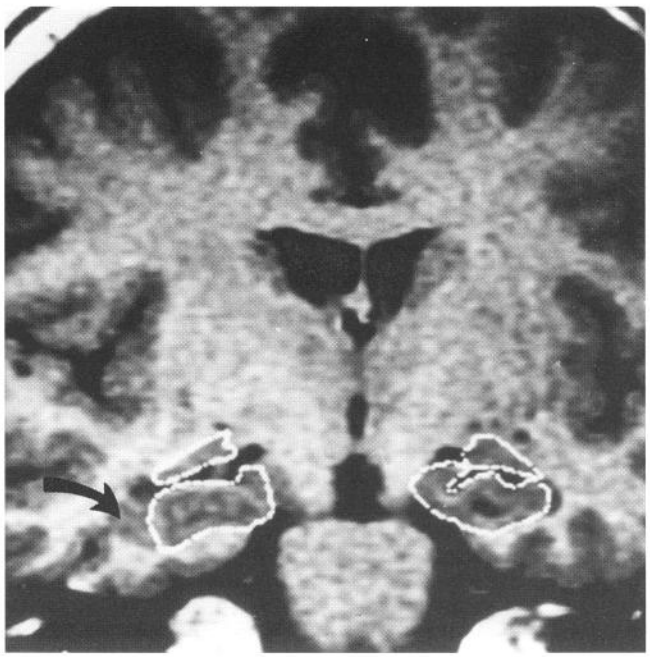

Figure 5.
Coronal MRI scan showing a moderate-sized area of heterotopic gray matter (arrow) adjacent to the head of the right hippocampus. The patient had complex partial seizures originating from the right temporal lobe. The two hippocampi (lower outlines) and amygdalae (upper outlines) are outlined and do not show atrophy of the right side.

vulsions in early childhood and more frequent secondarily generalized seizures. These findings were believed to support the concept that ictal fear is related to pathology of the amygdala and that both the amygdala and the hippocampus are important substrates of temporal lobe epilepsy.

Specificity of Volumetric Magnetic Resonance Imaging in Detecting Hippocampal Sclerosis. As mentioned above, MRI-based volumetric measurements of the hippocampus and amygdala appear to be very sensitive in lateralizing the epileptogenic region. A second question concerns the specificity of hippocampal and amygdaloid volume measurements. Some authors have suggested that the radiologic features of atrophy of medial temporal lobe structures are common in patients with complex partial seizures but also are seen frequently in other seizure types and can even occur in patients without epilepsy (143-145). Others have measured the specificity of volumetric MRI studies and obtained different values (89,146,147). The central question is whether frequent seizures originating at sites other than the hippocampus and amygdala can cause cell loss and subsequent atrophy of those structures. If so, volumetric studies of the hippocampus and amygdala would be less specific to the entities of hippocampal and amygdaloid sclerosis and would therefore be less valuable in distinguishing between seizures arising from medial temporal and extratemporal sites. Recently, investigators have begun to study this question.

In studying this question, investigators have looked at groups of patients with longstanding epilepsy arising from regions of the brain other than medial temporal lobe structures. Groups that have been studied include those with epilepsy caused by extratemporal structural lesions or extrahippocampal temporal lobe lesions, those with primary generalized epilepsy, and those with secondary generalized epilepsy.

Studies have shown that patients with epilepsy and extratemporal structural lesions have either no reduction in hippocampal volumes (83,148-150) (Figs. 2 and 4) or a very low incidence of so-called "dual pathology," a condition in which the patient has both hippocampal sclerosis and a potentially epileptogenic structural lesion (151-153). These latter studies found an incidence of dual pathology ranging from 7 to 10.5%.

Preliminary studies in patients with extrahippocampal temporal lobe lesions and epilepsy also indicate a very low incidence of hippocampal and amygdaloid atrophy (152) (Fig. 5). This study showed that dual pathology was present in 13% of these patients. Furthermore, in a large-scale multicenter study recently completed, we studied 167 patients with extrahippocampal temporal and extratemporal lesions and found only 25 patients (15%) with dual pathology (154,155).

Similarly, recent reports in patients with longstanding primary generalized epilepsy (156,157) and secondary generalized epilepsy (158,159) failed to show reduction of hip-

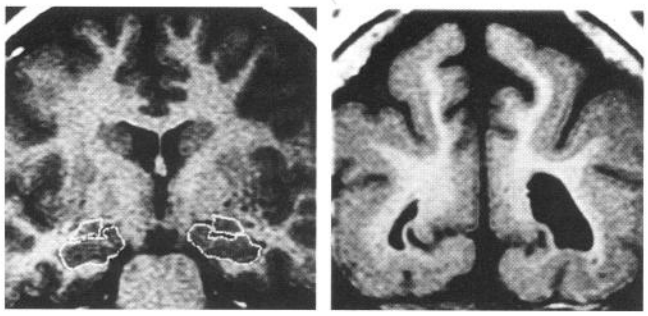

Figure 6.
Coronal MRI scans showing normal and symmetric hippocampal and amygdaloid volumes (outlined bilaterally) on the left and bilateral parieto-occipital pachygyria on the right in a patient with secondary generalized epilepsy.

pocampal or amygdaloid volumes in any of the patients (Fig. 6).

These data, taken together, show a very low incidence of hippocampal and amygdaloid atrophy in patients with epilepsy and extrahippocampal temporal or extratemporal structural lesions. When this occurs, care must be taken in planning surgical therapy for the patient's epilepsy if it is intractable. Patients with primary and secondary generalized epilepsy also failed to exhibit significantly reduced hippocampal and amygdaloid volumes, even when their epilepsy was of longstanding duration. Therefore, it appears that significant reduction in hippocampal and amygdaloid volumes is a specific marker for hippocampal and amygdaloid sclerosis (160).

Volumetric Magnetic Resonance Imaging in Bilateral Temporal Lobe Epilepsy. Patients who have seizures originating from each temporal lobe independently are a particularly difficult group to deal with in a surgical epilepsy program. If a significantly greater number of seizures arise from one side compared with the other, some centers perform a temporal lobectomy on that side with the hope of significantly improving the patient's clinical situation. Preliminary studies seem to indicate that volumetric MRI may be useful in helping to make those surgical decisions (77-79,161-167). Even though bilateral hippocampal atrophy may be present on volumetric MRI studies, if the more profoundly atrophic side coincides with the side of more frequent seizure onset, temporal lobectomy may prove exceedingly helpful in controlling the patient's seizures. Obviously, when dealing with bilateral hippocampal atrophy, one must use the absolute hippocampal volumes and their relationship to the normal control group rather than the ratio of one side to the other. If one uses the hippocampal ratio only, no asymmetry or abnormality may be detected.

Postoperative Volumetric Magnetic Resonance Imaging Analysis. Recently, preliminary studies using postoperative volumetric MRI analysis in temporal lobectomy patients have been reported (168-170). Although the findings are preliminary, it appears that postoperative volumetric MRI studies may be helpful in determining the extent of amygdaloid and hippocampal resection. These data may be useful in the future to help guide our decisions concerning epilepsy surgery.

Magnetic Resonance Imaging of the Hippocampus: Qualitative vs. Quantitative Assessment. Although a number of studies have shown quantitative MRI-based volumetric analysis of the hippocampus and amygdala to be highly sensitive and specific in the identification of hippocampal sclerosis, simple qualitative visual analysis of properly acquired MR images is also quite sensitive in this task. A few studies have been completed comparing quantitative volumetric MRI of the hippocampus with qualitative visual analysis of MR images for the signs of hippocampal sclerosis. In the original work by Jack et al (89), the investigators found only slightly increased sensitivity with volumetric MRI compared with qualitative assessment of the images (76 vs. 71%, respectively). However, more recent investigations using higher resolution MR techniques have found volumetric MRI measurements to be significantly more sensitive than visual inspection alone (171-173). Cendes et al (171, 173) found that volumetric MRI showed a sensitivity of 92% compared with 56% for qualitative visual inspection. Similarly, Reutens et al (172) showed that volumetric MRI was at least 20% more sensitive than qualitative inspection. Therefore, it appears that there is a significant improvement in detection rate with volumetric MRI, although it is much more time consuming and must be done correctly to be reliable and accurate. As Jack has noted, the greatest utility for volumetric MRI may be in the field of clinical research (76).

Recent investigations using more high-resolution magnetic resonance techniques have found volumetric magnetic resonance imaging measurements to be significantly more sensitive than visual inspection alone.

New Techniques – In the past few years several new MRI-based techniques have been developed and are beginning to be applied to the study of patients with epilepsy. These include T2 relaxometry, functional MRI (fMRI), echo planar imaging, and diffusion-weighted imaging. Of these, the first two modalities have been used most often in the study of patients with epilepsy.

T2 Relaxometry. T2 relaxometry provides a quantitative, objective means of detecting and assessing the abnormal T2-weighted signal intensity that is present in the

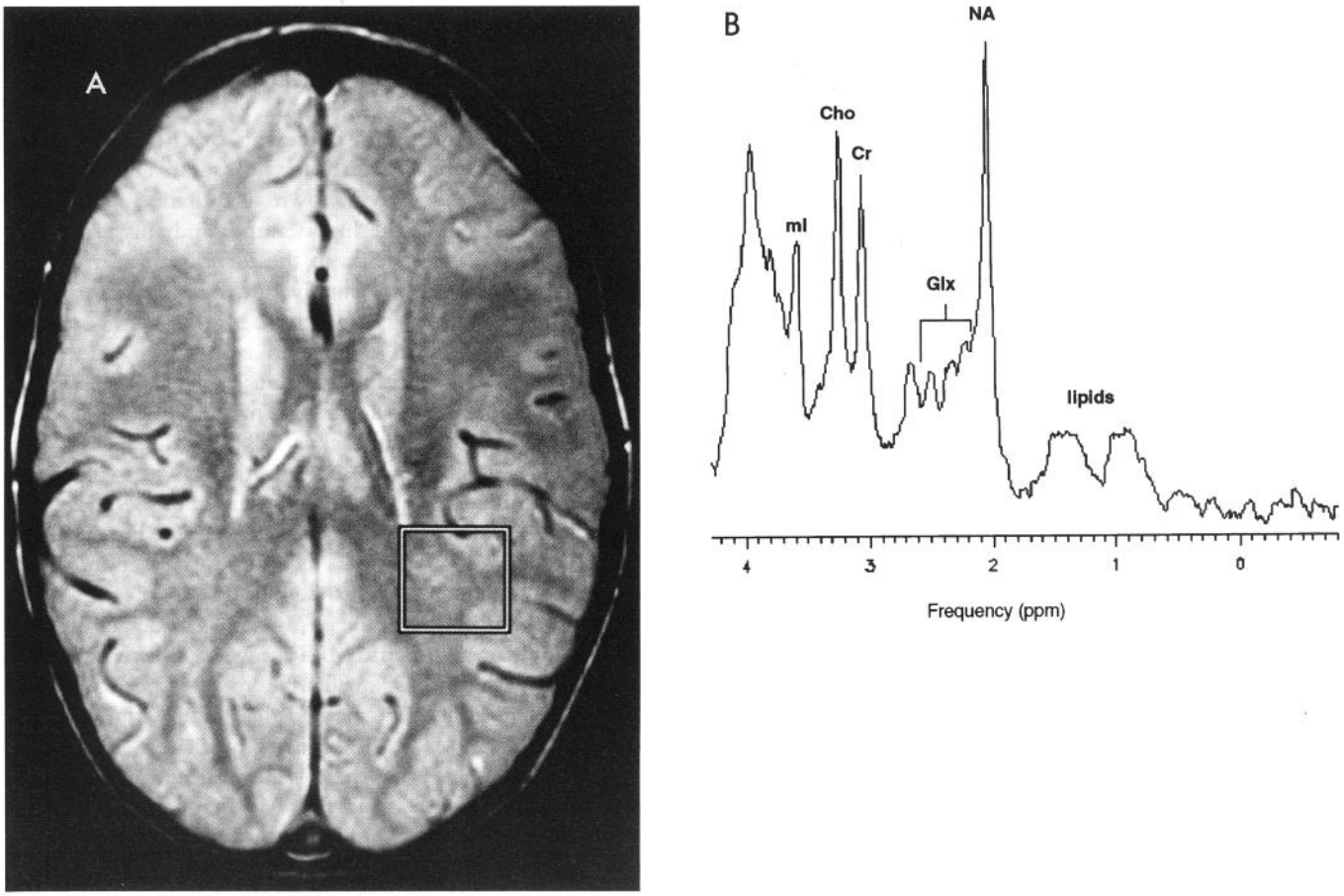

Figure 7.
A, Proton density axial MR image (spin echo TE/TR, 30/2500). The white box in the left parietal area represents the region of interest from which the proton MR spectrum in B was acquired. *B*, Single voxel proton MR spectrum (Stimulated Echo Acquisition Method: TE/TM/TR, 30/13.7/2000) acquired from the region of interest indicated on the above image. Abbreviations are as follows: NA = N-acetyl compounds, primarily N-acetyl-aspartate, CR = creatine, Cho = choline, mI = *myo*-inositol, Glx = glutamine and glutamate.

hippocampus and amygdala in patients with hippocampal and amygdaloid sclerosis. This increased signal may be difficult to detect qualitatively by visual inspection alone, and T2 relaxation measurements may prove to be very useful in the noninvasive evaluation of patients with medically intractable temporal lobe epilepsy (174-179). The technique may be quite informative and sensitive in its detection of bilateral hippocampal sclerosis, and in that way it may be complementary to electrophysiologic studies and volumetric MRI (174-177). Although special technical specifications must be considered, the technique will probably become easier to use as experience accumulates.

Functional Magnetic Resonance Imaging. fMRI detects signal changes in brain that accompany regional changes in cerebral blood flow related to neuronal activity. In normal brain, functional MRI shows these changes in appropriate functional areas of the cerebrum in response to motor, sensory, or language tasks that activate these areas (180-182). This technique is under study to determine whether it can be used in patients with epilepsy to demonstrate functional areas of the brain, detect abnormalities in cortical function in partial epilepsy, and even capture and map cortical activation during seizures (183-186). In this manner, fMRI may be able to replace or complement the intracarotid amobarbital (Wada) procedure in the future by demonstrating language and memory lateralization noninvasively. fMRI will probably not replace PET and SPECT studies, however, because its use during seizures will most likely be limited to rare patients with frequent seizures with minimal or no motor manifestations. Nevertheless, it seems likely that fMRI will become a powerful research tool with significant clinical application in the next several years.

MAGNETIC RESONANCE SPECTROSCOPY

In vivo MRS is a tool that has recently been developed to noninvasively study cerebral metabolites (for an excellent review article, see Ref. 187). MRS uses the same basic instrument as a conventional MRI system, but differs in that

it uses special pulse sequences (combinations of radiofrequency and gradient pulses) to acquire either localized metabolic profiles or spectroscopic images of the brain. Clinical research studies using MRS technology to investigate its potential utility in epilepsy have focused primarily on proton (^{1}H)- and phosphorus (^{31}P)-containing brain metabolites. In vivo ^{1}H MRS technology can provide noninvasive concentration measures of choline, creatine (Cr), N-acetyl-aspartate (NAA), lactate, *myo*-inositol, glutamine, glutamate, and lipids in the human brain (Fig. 7). The NAA resonance has been the subject of considerable recent investigation and has been demonstrated to be a putative specific neuronal marker not found in mature glial cells (188). In vivo ^{31}P MRS of the brain provides concentration measures of phosphocreatine (PCr), adenosine triphosphate, inorganic phosphate (Pi), phosphomonoesters (PMEs), and phosphodiesters. In addition, ^{31}P MRS provides a noninvasive measure of the intracellular pH by determining the chemical shift of the Pi resonance referenced to PCr.

Recent studies in temporal lobe epilepsy patients using ^{1}H MRS, with both single voxel techniques (189,190) and spectroscopic imaging methods (191-193), have consistently revealed a decreased absolute NAA concentration and/or a decreased NAA/Cr ratio interictally in the region of the epileptogenic focus compared with the contralateral temporal lobe. One of these studies (193) reported that the NAA/choline ratio was the most sensitive index for localizing temporal lobe abnormalities. A ^{1}H MRS study of frontal lobe epilepsy using a spectroscopic imaging technique reported a decreased NAA/Cr ratio in the epileptogenic frontal lobe compared with the contralateral frontal lobe in all eight patients examined (194). Limited ^{1}H MRS studies of other epileptic disorders including epilepsia partialis continua, Rasmussen's syndrome, herpes encephalitis, Sturge-Weber syndrome, neuronal migration abnormalities, and idiopathic complex partial seizures all uniformly demonstrate a common finding of decreased absolute NAA concentration and/or decreased NAA/Cr ratio in the region of seizure focus (189,190,195). The in vivo ^{1}H MRS findings of decreased NAA concentration have been confirmed by high-resolution ^{1}H nuclear magnetic resonance spectroscopy studies (196) of epileptogenic cortical tissue obtained during epilepsy surgery, and pathological examination indicates neuronal loss in these regions, thus supporting the notion that decreased NAA concentration may be a marker of neuronal loss. In several of the studies discussed above, the observation of a lactate resonance in the MRS metabolic profile was reported when a patient experienced a seizure immediately before or during the MRS examination. This finding of increased regional lactate concentration is probably indicative of anaerobic glycolysis in the epileptogenic region.

^{31}P MRS studies of temporal lobe epilepsy using both single voxel examinations (197,198) and spectroscopic imaging examinations (199, 200) have consistently observed increased intracellular pH, increased Pi concentration, decreased PCr/Pi ratio, and decreased PME concentration in the area of seizure focus when performed in the interictal state. In a series of ^{31}P MRS studies from one group (197,199,200), temporal lobe epileptogenic foci were localized in all 18 patients studied. In one study of frontal lobe epilepsy using ^{31}P spectroscopic imaging (201), eight patients were studied in whom MRI and/or 2-deoxy-2[^{18}F]fluoro-D-glucose (18-FDG) PET failed to provide lateralizing information. All eight patients showed interictal alkalosis in the epileptogenic frontal lobe compared with the contralateral frontal lobe, whereas seven of the eight patients showed decreased PME levels in the ipsilateral frontal lobe compared with the contralateral side.

These preliminary clinical research findings suggest that in vivo MRS will likely become a valuable adjunctive tool for evaluation and management of patients with epilepsy. However, it is clear that studies involving larger numbers of patients and comparisons of ^{31}P and ^{1}H MRS with EEG, MRI, and PET are necessary to determine the sensitivity of this tool for detecting focal abnormalities associated with epilepsy.

In addition to the lateralization and localization of seizure foci in epilepsy, many investigators are now beginning to use the information gathered by in vivo MRS technology to investigate the underlying pathophysiology and neurochemical mechanisms of epileptogenesis. There is growing enthusiasm among clinical epileptologists and basic scientists that the use of this tool may yield valuable new information for the treatment and management of this disease.

POSITRON EMISSION TOMOGRAPHY

PET is a noninvasive imaging method that can be used to measure local chemical functions in various body organs. The application of PET in the evaluation of patients with epilepsy has had a significant impact on management, particularly when the epilepsy is refractory to pharmacotherapy and surgical intervention is being considered.

The success of epilepsy surgery is largely due to the identification of discrete epileptogenic foci that are lateralized to, or localized in, one hemisphere. In infants, particularly, the clinical and EEG features of seizures arising from a single focus are often difficult to differentiate from seizures that arise from multiple bilateral and diffuse foci. When the MRI scan fails to show a discrete lesion in the patient with intractable epilepsy and interictal and ictal scalp EEG localization is insufficient to permit surgery, the noninvasive localization of the epileptogenic focus by PET with the tracer FDG eliminates the need for chronic invasive EEG monitoring in the majority of children undergoing epilepsy surgery. By fulfilling a role similar to that of MRI when MRI fails to show a lesion, PET provides a useful guide to the type of resection to be performed. Furthermore, PET can provide an assessment of the functional integrity of brain regions outside the epileptogenic area.

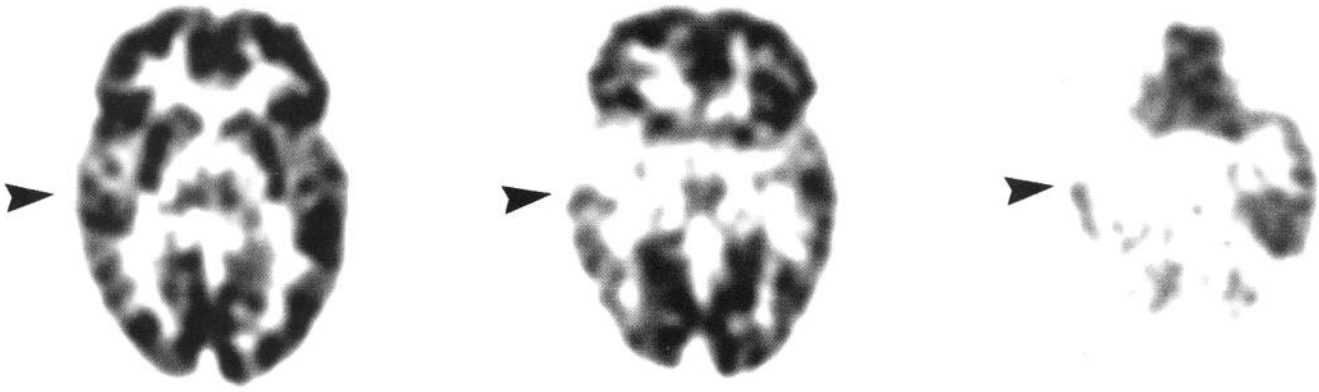

Figure 8.
PET scan of cerebral glucose metabolism of a patient with temporal lobe epilepsy, a nonlateralizing interictal EEG, and a normal MRI scan. Glucose metabolic activity is decreased in the right temporal neocortex (arrows).

Basic Concepts of Positron Emission Tomography Methodology

The PET technique uses a camera consisting of multiple pairs of oppositely situated detectors that are used to record the paired high-energy (511-KeV) photons traveling in opposite directions as a result of positron decay (202). Tracer kinetic models that mathematically describe physiological or biochemical reaction sequences of compounds labeled with positron-emitting isotopes permit a characterization of the kinetics and the mathematical expression for calculating actual rates of the biological process being studied (203). Because of the short half-life (minutes to hours) of the isotopes commonly used in PET, it is essential that the cyclotron used to generate these isotopes be situated either on-site or within 1 to 2 hours' driving distance from the PET scanning facility. The clinical and research applications of PET methodology have been steadily increasing, and more than 300 substrates and drugs labeled with positron emitters are available for the study of various biological functions in vivo (204). In the brain, PET has been applied in the study of local glucose and oxygen utilization, blood flow, protein synthesis, and neurotransmitter uptake and binding (205).

Temporal Lobe Epilepsy

In adults and children with temporal lobe epilepsy, studies performed with FDG-PET during the interictal period have identified areas of decreased glucose utilization (Fig. 8); these areas of "hypometabolism" correspond anatomically with pathologic and depth electrode EEG localization of epileptogenic lesions (206,207). Although ictal PET studies often reveal complex patterns of increased glucose metabolism, focal hypermetabolism may sometimes be seen on interictal PET scans in the presence of an active focal epileptiform discharge on the EEG (208).

The sensitivity of PET in identifying the epileptogenic focus in patients with temporal lobe epilepsy is approximately the same as that of depth electrode recording. However, PET is far less costly and is not associated with the morbidity and mortality of electrode implants. The application of FDG-PET in the presurgical evaluation of temporal lobe epilepsy patients has led to a significant reduction in the need for invasive EEG monitoring (209,210). The sensitivity of FDG-PET may be further increased by activation procedures such as performance of a speech discrimination task during the tracer uptake period (211), but these preliminary findings require further study and confirmation. On the other hand, recent advances in analysis techniques of MRI have shown that quantitative MRI is very sensitive in detecting hippocampal atrophy in patients with temporal lobe epilepsy and will probably eliminate the need for invasive EEG monitoring in the majority of patients with temporal lobe epilepsy. Furthermore, with the greater availability of MRI compared with PET, it is likely that in the future PET will be reserved only for those cases in which MRI fails to provide the necessary localization.

The presence of temporal lobe hypometabolism may provide prognostic information as to the success of temporal lobectomy. Radtke et al (212) found that both the degree and extent of temporal lobe hypometabolism correlated with a favorable surgical outcome. However, at least two other studies have not found any differences in outcome between patients who showed temporal lobe hypometabolism on PET and patients with a normal or nonlocalizing PET pattern (33,213). An important recent finding relating temporal lobe hypometabolism to prognosis was that memory impairment, as determined by the intracarotid amobarbital pro-

cedure, was never present contralateral to the side of hypometabolism but was found ipsilateral to hypometabolism in as many as 65% of patients (214).

Attempts have been made, using FDG-PET, to distinguish the metabolic patterns between seizure onset from medial and lateral temporal lobe regions. One distinguishing feature is that, in patients with hippocampal sclerosis, glucose metabolism in the entire temporal lobe was much lower than in patients who had lateral temporal onset of seizures, which were associated with only mild hypometabolism in the medial temporal region (215).

Extratemporal Lobe Epilepsy

There are very few studies that have evaluated the use of FDG-PET in frontal lobe epilepsy occurring in older children and adults. The general experience with seizures of frontal lobe origin is that, in the absence of a discrete lesion or focal atrophy in the frontal lobe, the PET results are usually normal. However, this was not the experience of Swartz et al (216), who studied 22 patients with frontal lobe epilepsy. In their study, 32% showed CT abnormalities and 45% showed MRI abnormalities. Focal, regional, or hemispheric hypometabolism was seen in 64% of patients and correlated with electroclinical ictal localization. These findings have not been confirmed by other investigators.

The sensitivity of positron emission tomography in identifying the epileptogenic focus in patients with temporal lobe epilepsy is approximately the same as that of depth electrode recording.

When onset of frontal lobe seizures is in the neonatal period or in infancy, an underlying structural lesion is often present even when the MRI result is normal. Under these circumstances, the FDG-PET can be quite useful in defining an area of hypometabolism that correlates with both the extent of microdysgenesis (217) and the area of epileptogenicity (218).

Infantile Spasms

PET studies of cerebral glucose utilization have revolutionized the management of infants with intractable spasms and altered our concepts regarding the pathophysiology of infantile spasms. Most infants diagnosed with "cryptogenic" spasms have, in fact, focal cortical regions of decreased (Fig. 9) or increased glucose utilization on PET. Focal ictal and/or interictal EEG abnormalities correspond to the PET focus in most of these cases (219). In infants with hypsarrhythmia, these focal EEG abnormalities either precede or follow the presence of hypsarrhythmia in the evolution of the infants' EEGs. When a single region of abnormal glucose utilization corresponding to the EEG focus is apparent on PET and the seizures are intractable, surgical removal of the PET focus results not only in seizure control but also in complete or partial reversal of the associated developmental delay. Neuropathological examination of the resected tissue in the children who underwent surgery reveals that the epileptogenic zone is typically a previously unsuspected area of cortical dysplasia (219,220).

Infantile spasms have been considered to be generalized seizures resulting from complex cortico-subcortical interactions. There has been considerable debate as to whether the spasms originate in the brain stem, basal ganglia, or cortex. PET studies have shown not only that cortical metabolic lesions are common in infants with spasms but also that the lentiform nuclei and brain stem are often metabolically prominent. Although the brain stem has been suspected to be involved in the generation of spasms, the lentiform nuclei findings are new. This constellation of findings suggests that spasms result from focal or diffuse cortical abnormalities interacting with subcortical structures. Bilateral activation of the lentiform nuclei is consistent with the observation that infantile spasms are clinically symmetric even when focal cortical lesions are present. Thus, PET studies have significantly increased our understanding of the pathophysiology of infantile spasms. Based on these findings, the potential neuronal circuitry involved in the generation and propagation of infantile spasms has been proposed (221).

Other Childhood Epilepsy Syndromes

PET scanning of cerebral glucose utilization has been applied in the study of a number of childhood epilepsy syndromes other than infantile spasms. In children with Lennox-Gastaut syndrome, PET has provided a new classification based on metabolic anatomy. Four metabolic subtypes have been identified: unilateral focal, unilateral diffuse, and bilateral diffuse hypometabolism and normal patterns of metabolism (222–224). These glucose metabolic patterns may serve as a useful guide in determining the type of surgical intervention in those patients with uncontrolled seizures. Interestingly, there were no differences in glucose metabolic rates between PET studies performed during continuous slow spike-wave activity and studies in which there was minimal epileptiform activity on the EEG (222). This finding was confirmed in a later study on the effects of generalized spike-and-wave discharges on glucose metabolism (225).

In children and adults with advanced Sturge-Weber syndrome, PET typically reveals widespread unilateral hypometabolism ipsilateral to the facial nevus in a distribution that extends beyond the abnormalities depicted on CT. In con-

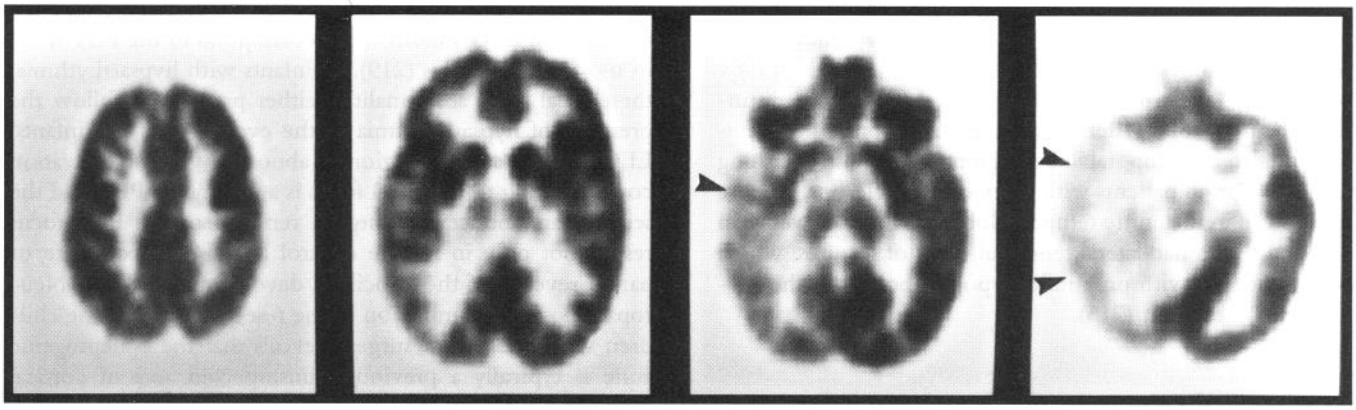

Figure 9.
PET images of cerebral glucose metabolism from an infant with intractable infantile spasms and a normal MRI scan. The PET scan shows decreased glucose metabolism in the right temporal and occipital cortex (arrows). Scalp EEG showed epileptiform activity localized to the general region of the PET abnormality. The infant underwent surgical resection of the epileptogenic cortex guided by PET and intraoperative corticography. Pathology revealed cortical dysplasia.

trast, small infants (< 1 year of age) with Sturge-Weber syndrome and recent seizure onset show a paradoxical pattern of increased glucose utilization in the cerebral cortex of the anatomically affected hemisphere on interictal PET (226). In Sturge-Weber syndrome patients with refractory epilepsy, PET has been useful both in guiding the extent of focal cortical resection (i.e., correlating better with intraoperative electrocorticography than CT or MRI) and in assessing candidacy for early hemispherectomy. Finally, PET provides not only a sensitive measure of the extent of early cerebral involvement in Sturge-Weber syndrome patients but also a means of monitoring disease progression (227).

Cortical tubers in tuberous sclerosis appear as hypometabolic areas interictally on PET scanning (228), presumably due to the simplified dendritic arborization within tubers. When the PET study is performed ictally, the tuber is seen as a hypermetabolic zone. Some hypometabolic regions on PET do not correspond to abnormalities on CT and MRI scans and may either represent small tubers or be related to epileptogenic mechanisms.

Hemimegalencephaly is a rare developmental brain malformation characterized by congenital hypertrophy of one cerebral hemisphere and ipsilateral ventriculomegaly. When the epilepsy is medically uncontrolled, cerebral hemispherectomy is recommended. However, irrespective of seizure control postoperatively, hemimegalencephalic children as a group have a worse developmental outcome compared with other children who have undergone hemispherectomy for Sturge-Weber syndrome or chronic focal encephalitis of Rasmussen. PET studies of cerebral glucose metabolism have indicated that the worse developmental outcome in hemimegalencephaly is related to the presence of focal areas of cortical dysfunction in the remaining hemisphere and that preoperative assessment of the integrity of the less affected hemisphere with PET may provide important prognostic information (229).

An FDG-PET study during sleep in three children with acquired epileptic aphasia (Landau-Kleffner syndrome) confirmed the general notion that this condition is heterogeneous. Metabolic disturbances consisting of hypermetabolism or hypometabolism were seen in the temporal lobes during sleep and were right-sided, left-sided, or bilateral (230).

Effects of Antiepileptic Drugs on Cerebral Glucose Utilization

PET with FDG has been used to evaluate the effects of a number of antiepileptic drugs on regional cerebral glucose metabolism in order to gain a better understanding of mechanisms of action and toxicity. Barbiturates such as phenobarbital and primidone had a large effect on cerebral glucose metabolism in seven of eight cortical regions analyzed, with a mean reduction of 37% (231). Phenytoin decreased overall cerebral glucose metabolism by 13%, with parietal and frontal cortex showing significant reductions (232). Carbamazepine caused a 12% mean reduction of cerebral glucose metabolism, with the most significant changes in bilateral superior frontal, left parietal, right superior temporal, right caudate, and left cerebellar regions (233). Valproate reduced global cerebral glucose metabolism by 22% and significantly decreased metabolic rates in 15 of 26 regions analyzed (234). None of these studies examined the relationship between brain metabolism effects and neuropsychological function.

Neurotransmitter Receptor Positron Emission Tomography

As illustrated above, the application of FDG-PET in the study of epilepsy has been rewarding and has altered management in many instances. However, FDG is but one of many potential chemical probes that can be applied quanti-

tatively with PET technology. Based on several preliminary studies, there is now considerable enthusiasm for further developing and applying PET to examine a number of neurotransmitter receptors believed to be important in epileptic mechanisms.

Opioid mechanisms in the brain are believed to play an important role in epilepsy, particularly postictal phenomena (235). The application of PET using ^{11}C-carfentanil, a ligand with high affinity for mu-opiate receptors, in patients with temporal lobe epilepsy has shown that opiate receptor binding is increased in the temporal neocortex ipsilateral to the seizure focus compared with the opposite side, and this correlated directly with a decrease of glucose metabolism. No asymmetries of receptor binding were observed in medial temporal structures. The authors suggested that the observed temporal neocortical increase may represent a tonic inhibition of epileptogenicity in surrounding structures (236). Further studies from the same group of investigators have shown that increased ^{11}C-carfentanil binding in temporal neocortex is associated with decreased binding in amygdala ipsilateral to the seizure focus. Moreover, when PET was performed with ^{11}C-diprenorphine, which binds not only to mu-opiate but also to kappa- and delta-opiate receptors, there were no significant differences in binding between the epileptogenic focus and the contralateral temporal lobe (237).

Using ^{11}C-doxepin, an antidepressant with a high affinity for histamine H1 receptors, Iinuma and colleagues (238) documented increased binding in the temporal neocortex ipsilateral to the epileptogenic focus in eight of nine patients with complex partial seizures of temporal or frontal lobe origin. Because histamine in the brain is involved in termination of seizures and may function as an endogenous anticonvulsant, the investigators postulated that the increased binding may represent a defensive mechanism counteracting the spread of epileptic discharges.

PET studies of the benzodiazepine receptor using the antagonist ^{11}C-Ro 15-1788 (flumazenil) have shown that patients with partial epilepsy have a significantly reduced binding in the epileptic focus (239). In patients with generalized epilepsy, no significant changes in binding could be demonstrated in comparison with brain regions outside of the epileptogenic focus in patients with partial epilepsy (240). Whether there is an absolute decrease in benzodiazepine receptor binding in generalized epilepsy compared with controls remains to be determined.

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY

SPECT is a noninvasive functional imaging technique that uses simpler and less expensive equipment than PET. It provides tomographic imaging through the use of either a single rapidly rotating gamma camera or multiple cameras to detect and reconstruct gamma ray emissions (241). Because of the longer half-life of SPECT isotopes compared with isotopes used in PET and the readily available equipment, SPECT is suited for even the smallest hospitals and clinics. The isotopes can be obtained commercially and can be stored on site. However, the spatial resolution of SPECT images is approximately half that achieved with PET, a distinction that is particularly relevant in pediatric studies. The localizing value of SPECT in children with epilepsy usually is limited to detecting the involved lobe. Furthermore, SPECT techniques are semiquantitative at best, whereas PET is fully quantitative.

In brain studies, SPECT has been used primarily to provide an index of cerebral blood flow. Radioactive probes developed for this purpose have included the iodoamines, xenon, and technetium-99m hexamethyl propylene amine oxime (^{99m}Tc-HMPAO). When ictal and postictal localization of seizure foci is desired, SPECT studies are particularly useful for several reasons. For example, the iodoamines freely pass through the blood-brain barrier and reach peak concentrations in the brain approximately 20 minutes after intravenous administration. The iodoamine hydroxyiodobenzyl propanediamine reaches 75% of its peak brain concentration at 2 minutes after injection. Scanning of the brain can be initiated at leisure after the brain uptake phase, because the trapped agent remains relatively stable for at least 1 hour and the isotopes used in SPECT have a rather long half-life (e.g., ^{123}I has a half-life of 13 hours). In contrast, because of the short half-life of PET isotopes (e.g., 108 minutes for ^{18}F and 20 minutes for ^{11}C), it is extremely difficult to achieve planned ictal and postictal PET studies. Furthermore, ictal PET studies with FDG typically include a prolonged postictal phase as well as the ictus to yield a summation of the two phases, and they are therefore often difficult to interpret.

Partial Epilepsy

After the demonstration of interictal hypometabolism and ictal hypermetabolism in the seizure focus with PET technology, a number of investigators attempted to replicate these findings with SPECT determinations of cerebral perfusion. Magistretti et al (242) showed ictal hyperperfusion of the seizure focus in a single patient studied with ^{123}I-iodoamphetamine SPECT. Using ^{133}xenon SPECT, Bonte et al (243) showed interictal focal hypoperfusion in 12 of 18 patients with epilepsy and enhanced flow to an active seizure focus. In another study on 50 patients with partial seizures, the same group of investigators reported a significant correlation between the location of interictal SPECT hypoperfusion and the location of neuropsychological deficits revealed by the Halstead-Reitan battery (244). The roles of interictal, ictal, and postictal SPECT studies in epilepsy have all been investigated with regard to clinical utility.

There have been many interictal SPECT studies performed on patients with epilepsy. Using ^{123}I-iodoamphetamine and SPECT, Denays et al (245) evaluated 14 children with a variety of seizure types. Of the 9 children who had normal CT scans, 5 had SPECT abnormalities including fo-

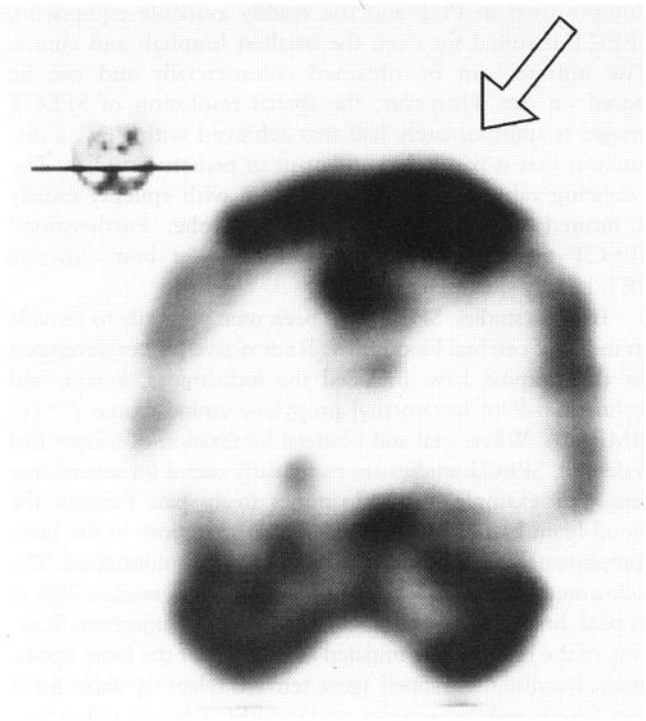

Figure 10.
SPECT image from a 7-year-old boy with intractable partial epilepsy. Coronal view of an ictal brain SPECT scan after intravenous injection of ^{99m}Tc-HMPAO 3 minutes after seizure onset demonstrates a focus of intensely increased perfusion in the left superior parietal cortex (arrow).

cal hypoperfusion, diffuse hemispheric hypoperfusion, multifocal and bilateral hypoperfusion, and focal hyperperfusion. Children with normal SPECT scans had a better overall prognosis than those with blood flow abnormalities in this study. Also using ^{123}I-iodoamphetamine, Dietrich et al (246) reported that SPECT revealed focal hypoperfusion in 21 of 23 patients with complex partial seizures, 15 of whom had good correspondence between SPECT and EEG foci. Four patients had multifocal SPECT abnormalities, and 2 had discordance between SPECT and EEG localization. Ryvlin et al (247) found that, in patients with temporal lobe epilepsy, ^{99m}Tc-HMPAO SPECT hypoperfusion of the temporal lobe was more frequently seen when the MRI showed a nonspecific abnormality than when the MRI was normal. All 18 patients in this latter study had normal CT scans. In another ^{99m}Tc-HMPAO SPECT study of 14 children with frequent seizures, the typical finding in 11 patients with partial seizures and secondary generalization was a single hypoperfused area. The 3 children with Lennox-Gastaut syndrome had multiple areas of hypoperfusion and a worse clinical outcome. SPECT was more sensitive than EEG, CT, or MRI in detecting abnormalities (248).

Interictal SPECT has also been used in children with less malignant types of seizures. One such study showed that 2 children with complex febrile convulsions among 19 children presenting with febrile convulsions had focal perfusion abnormalities on interictal SPECT using ^{99m}Tc-HMPAO. Of the 17 children who had simple febrile convulsions, 9 also had focal perfusion abnormalities on SPECT. Abnormal perfusion typically involved frontotemporal regions and was more often seen in children with EEG abnormalities and in those studied within 12 days of the convulsion (249).

Ictal SPECT appears to be more sensitive in detecting the epileptic focus than interictal studies in both temporal lobe and extratemporal epilepsy (Fig. 10). One group of investigators performed hydroxyiodobenzyl propanediamine SPECT on 16 patients with refractory complex partial seizures, and they were able to show the hyperperfused epileptogenic focus in 13 of 14 patients who had a unilateral temporal seizure onset. However, in the 2 patients with bitemporal EEG foci, SPECT showed bilateral multifocal areas of increased blood flow that were difficult to interpret (250). Ictal SPECT with ^{99m}Tc-HMPAO has proven to be useful in evaluating epilepsy with temporal and frontocentral onset, showing hyperperfusion that corresponded to EEG and structural localization in six of nine patients (251). In patients who exhibit ictal dystonia in one limb during a seizure, relative hyperperfusion of the basal ganglia contralateral to the side of dystonia was seen. Basal ganglia hyperperfusion was most marked if the tracer was injected during the dystonic episode (252). Harvey et al (253) found that ictal studies were informative in 16 of 17 studies in 14 of 15 children with temporal lobe epilepsy, corresponding well with ictal EEG, MRI, and pathology. In contrast, temporal lobe hypoperfusion seen interictally often proved to be difficult to interpret because it tended to be less well localized and was sometimes bilateral.

Marks et al (254) found ictal ^{99m}Tc-HMPAO SPECT to be a valuable tool in the localization of extratemporal epileptic foci. A well-circumscribed area of increased perfusion was the most common finding and was particularly useful in patients with nonlocalizing ictal EEG. Similarly, in two epileptic children with focal cortical dysplasias in the frontal regions and nonlocalizing EEG, ictal ^{99m}Tc-HMPAO SPECT proved to be invaluable in providing the necessary localizing data to proceed to surgical resection (255).

Postictal SPECT studies have also been found to be superior to interictal SPECT by some investigators (256). Seventy-eight seizures in 51 patients with temporal lobe epilepsy were studied with HMPAO SPECT, with increased uptake mainly in the anteromedial temporal region seen in 83% of patients during the first several minutes after the seizure. In 80% of studies, the medial temporal hyperperfusion was accompanied by hypoperfusion in the lateral temporal cortex and other areas of the ipsilateral cortex corresponding to both degree and extent of postictal slow wave activity on the EEG. This postictal hypoperfusion may last up to 20 minutes. As a result of postictal SPECT, the unilateral seizure focus could be localized correctly in 31 of 45 patients (257).

Other applications of SPECT in epilepsy have included the evaluation of the status of hemispheric blood flow during

the Wada test. In one such study, Ryding et al (258) showed that the timing of ^{99m}Tc-HMPAO injection should be approximately 30 seconds after the onset of barbiturate effect in order to best visualize the low-flow regions. Acute cerebellar hypoperfusion contralateral to the side of barbiturate injection was also detected, indicating a diaschisis phenomenon.

Epilepsy Syndromes

As in the case of PET, there have been many studies on the use of brain SPECT in various epilepsy syndromes of infancy and childhood, some of which will be reviewed here. In two children with hemimegalencephaly, iofetamine SPECT performed interictally showed a similar pattern of decreased perfusion in the malformed hemisphere (259), despite the very different EEG findings between the two patients, implying different prognoses as suggested by Paladin et al (260).

Chiron et al (261) have studied patterns of interictal brain perfusion in children with Sturge-Weber syndrome using ^{133}xenon SPECT. In 10 such patients, they found areas of decreased perfusion corresponding topographically to the CT scan abnormality. However, they documented focal hypoperfusion with SPECT in another three patients with no obvious focus on CT scan. The investigators suggested that focal hypoperfusion may have been the result of chronic ischemia and postictal mechanisms.

Ictal single photon emission computed tomography appears to be more sensitive in detecting the epileptic focus than interictal studies in both temporal lobe and extratemporal epilepsy.

Focal areas of cortical hypoperfusion have been detected with ^{133}xenon SPECT in patients with West syndrome (262). In an additional study by the same group of investigators, it was shown that mean cerebral blood flow decreased just after steroid treatment (263). In addition, areas of hypoperfusion appeared to be static in longitudinal studies, as had been shown with FDG-PET (219), whereas frontal regions of increased perfusion tended to diminish as the spasms became controlled. Yet another study from the same group showed that focal SPECT hypoperfusion in the parieto-occipital region is often associated with visual inattention at the time when the infants present with West syndrome and with long-term cognitive compromise (264). This latter finding is of particular importance when focal cortical resection is being considered as a treatment option in the setting of intractable infantile spasms (219,220).

Neuroreceptor Studies with Single Photon Emission Computed Tomography

Compared with PET, there has been relatively little success in the development of suitable SPECT probes for the evaluation of neurotransmitter receptor abnormalities in epilepsy. In one study, muscarinic cholinergic receptor imaging with ^{123}I-iododexetimide and SPECT in four patients with complex partial seizures revealed a 40 $\pm$ 9% (mean $\pm$ SD) decrease in hippocampal binding compared with the contralateral hippocampus (265).

COMPARISON OF COMPUTED TOMOGRAPHY, MAGNETIC RESONANCE IMAGING, POSITRON EMISSION TOMOGRAPHY, AND SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY

A number of studies have compared the ability of various imaging modalities to localize the area of epileptogenicity in the brain. For the most part, these comparative studies were performed on patients with refractory partial seizures being evaluated for surgical treatment.

Among 35 patients with intractable complex partial seizures and nonfocal CT, Sperling et al (15) found lesions on MRI in 7; 3 of these also had FDG-PET studies, which were normal in all. Of the 18 patients with hippocampal sclerosis on pathology, all had normal MRI results, but 10 had temporal lobe hypometabolism. It should be pointed out that this study was conducted before the application of MRI-based volumetric measurements of the hippocampus.

Among 20 children with partial epilepsy who had surgery, CT findings correlated with EEG foci in 14. MRI was more sensitive than CT and correlated with EEG foci in 13 of 14 children who had the procedure performed. ^{99m}Tc-HMPAO SPECT performed interictally showed cortical perfusion abnormalities that correlated with EEG foci in 14 of 20 children, whereas the combination of interictal and postictal SPECT studies detected the seizure focus in 16 of 20 (266).

Latack et al (16) compared CT, MRI, and FDG-PET in 50 patients with partial seizures, 4 of whom had surgery. Focal abnormalities were detected by CT in 13 and by MRI in 23 of the 50 patients. All of the 10 CT lesions were also detected by MRI. Only 14 patients were evaluated with FDG-PET; of these, metabolic asymmetries were present in 10 patients, 7 of whom had a structural lesion on MRI.

The study of Ryvlin et al (267) compared interictal FDG-PET with ^{99m}Tc-HMPAO SPECT in temporal lobe epilepsy. In 20 patients with clear unilateral temporal lobe foci on EEG, MRI showed nonspecific abnormalities in the epileptogenic temporal lobe in 10 and was normal in 10.

PET showed focal hypometabolism in 8, and SPECT showed focal hypoperfusion in 2 of the 10 patients with normal MRI results. Of the 10 subjects with abnormal MRI results, PET showed hypometabolism in all, whereas SPECT detected hypoperfusion in 9.

A retrospective analysis of 9 epileptic children with focal cortical dysplasia revealed MRI evidence of poor gray/white matter differentiation or pachygyria in 6, interictal focal hypoperfusion with HMPAO SPECT in 4, and postictal SPECT hyperperfusion in 2 (268).

The extent of epileptiform abnormalities determined with EEG generally exceeds that defined by MRI and in some cases may even involve regions remote from the structural abnormality. Similarly, interictal PET glucose hypometabolism exceeds the extent of anatomical abnormalities on CT and MRI (269). Nevertheless, it has been demonstrated that postoperative seizure control can usually be achieved with total resection of the lesion (53,270). Although there is some suggestion that high-resolution functional neuroimaging with PET provides a good estimate of the epileptogenic zone in children with underlying microscopic structural abnormalities (218), large studies comparing various imaging and electrographic modalities are not available. Furthermore, it is obvious that large-scale, prospective studies comparing all of the modalities used in the presurgical evaluation of patients with medically intractable epilepsy are needed to answer the questions concerning the relative sensitivity and specificity of each of these modalities in specific epileptic syndromes.

CONCLUSION

In this article, we have seen how the evolution of various neuroimaging modalities has had a significant impact on the diagnosis, treatment, and prognostic implications of epilepsy in patients of all ages. In many cases, imaging has led directly to new treatment options previously not considered. Of particular importance has been the development of MRI and functional neuroimaging techniques, which have opened up many research opportunities and led to increased surgical treatment approaches for the patient with intractable epilepsy. It should be emphasized that, in most cases, anatomical and functional neuroimaging modalities are complementary and should be carefully used in conjunction for the optimal management of the patient with epilepsy.

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