Seizures and Epilepsy: Structural Brain Imaging in Acute Seizures and Functional Neuroimaging in the Epilepsies

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Seizures and Epilepsy: Structural Brain Imaging in Acute Seizures and Functional Neuroimaging in the Epilepsies

Alexander M. McKinney, IV, MD, and Thomas R. Henry, MD

INTRODUCTION

Structural brain imaging is essential in the diagnosis of seizures and epilepsy, including evaluation of patients whose seizures have not been established as a manifestation of epilepsy. In the previous article in this series, we reviewed the cerebral anatomy, anatomical pathology, and structural imaging of the epilepsies. In this article, we review structural imaging in the acute evaluation of seizures and functional imaging in evaluation of chronic epilepsies. Magnetic resonance imaging (MRI) is the technique of choice for acute seizures (see the Table for a list of radiology and diagnostic imaging terms used throughout this article). In many instances, the evaluation of a first recognized grand mal seizure will lead to the initial diagnosis of epilepsy, and often a brain MRI abnormality clarifies this epilepsy diagnosis. In many other instances, the evaluation of a first recognized grand mal seizure will lead to the diagnosis of an acute symptomatic seizure, in which case the brain MRI is normal or shows abnormalities that are not specific to any of the epilepsies.

Functional imaging does not have an established role in the initial diagnosis of seizures and epilepsies, but is widely used in reevaluations of refractory epilepsies when surgical therapies are considered. The functional imaging modalities that are most often used in epilepsy surgery planning produce cerebral maps of interictal and ictal perfusion and interictal glucose metabolism. Distribution maps of neuronal and glial markers and of particular neurotransmitter and receptor systems also have been used in reevaluations of refractory epilepsies. While perfusion techniques of brain X-ray computed tomography (CT) are rarely used in clinical epileptology, functional MRI is widely applied. Ictal versus interictal perfusion mapping with single-photon emission computed tomography (SPECT) and interictal glucose metabolic mapping with positron emission tomography (PET) also are widely utilized. Mapping of specific neurochemicals is most often performed with magnetic resonance spectroscopy (MRS) and...
Structural Brain Imaging in Acute Seizures

The emergency department or intensive care unit evaluation of a first recognized grand mal seizure, with or without preceding nonconvulsive seizures, or of acute repetitive seizures and status epilepticus in chronic epilepsy, may disclose brain lesions or insults on acute imaging that are different from the chronic epileptogenic lesions.8,9 (Of course, emergency department evaluations often detect any of the chronic epileptogenic lesions reviewed in the preceding section.1) Some of these acute lesions require emergent neurosurgical intervention, while others will resolve and must be recognized mainly for accuracy of diagnosis and prognostication. Still others, such as limbic encephalitis, require urgent diagnosis and acute therapy, and also can evolve into chronically epileptogenic lesions. Current standards of care require brain CT or MRI in evaluation of a first seizure in an adult;10 imaging also is highly useful in children with new onset of seizures.11

ACUTE HYDROCEPHALUS

Acute hydrocephalus is manifested by dilatation of the temporal horns anteriorly and of the anterior recesses of the third ventricle, as well as by ventriculomegaly as seen in chronic hydrocephalus (Figure 1). These findings are visible on CT. Transependymal migration of cerebrospinal fluid (CSF) can be seen as periventricular on CT, but is more sensitively imaged with fluid-attenuated inversion recovery (FLAIR) on MRI. Also, in acute hydrocephalus there is diffuse effacement of cortical sulci. While ventriculomegaly occurs in cerebral atrophy, the cortical sulci become increasingly prominent as atrophy progresses (as a distinguishing feature from the sulcal effacement of acute hydrocephalus).

ACUTE LOBAR HEMORRHAGE

Acute lobar hemorrhages are hyperdense on CT and exert adjacent mass effect. Their appearance varies on MRI, based on the sequence. However, generally these are isointense to brain tissue on T1 sequences and are dark on T2, T2* (“T2-star”), and susceptibility-weighted imaging (Figure 2). Acute blood in the subdural and subarachnoid spaces has a similar appearance to acute blood in intracerebral locations (Figure 3 and Figure 4). Chronic hemorrhage appears dark on all sequences.

Table. Radiology and Diagnostic Imaging Terms

<table>
<thead>
<tr>
<th>Term</th>
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<tr>
<td>ADC</td>
<td>apparent diffusion coefficient</td>
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<td>DWI</td>
<td>diffusion-weighted imaging</td>
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<tr>
<td>FDG-PET</td>
<td>18F-fluorodeoxyglucose positron emission tomography</td>
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<tr>
<td>FLAIR</td>
<td>fluid-attenuated inversion recovery</td>
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<tr>
<td>MR</td>
<td>magnetic resonance</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>MRS</td>
<td>magnetic resonance spectroscopy</td>
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<td>SPECT</td>
<td>single-photon emission computed tomography</td>
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<td>SWI</td>
<td>susceptibility-weighted imaging</td>
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<td>T1WI</td>
<td>T1-weighted imaging</td>
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<td>T2WI</td>
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with PET. The physics of magnetic resonance (MR) and radionuclide emission signals, the biochemistry of radioligand preparation and analysis, and the technology of image acquisition and reconstruction are complex disciplines that are practiced by experts with whom epileptologists collaborate. Epileptologists who work in clinical imaging research would benefit from greater knowledge of the relevant imaging principles and techniques, which have been reviewed in several books.2–7

Structural Imaging in Evaluation of Acute Symptomatic Seizures and Acute Exacerbation of Chronic Epilepsy
LIMBIC ENCEPHALITIS

Limbic encephalitis is an acute-subacute clinicoradiologic syndrome that usually presents with partial-onset seizures and cognitive-affective disturbance of limbic system-mediated behaviors. The recognized etiologies of limbic encephalitis are herpes simplex, paraneoplastic disorders, and autoimmune injuries. The various etiologies of limbic encephalitis present with varying degrees of edema that is difficult to visualize on CT, unless coronal reconstructions are obtained by spiral CT acquisition. On MRI, images from diffusion-weighted imaging (DWI) may be positive (bright) within the first few days of onset, but the findings are best visualized on oblique coronal FLAIR images with medial temporal lobe edema (Figure 5). Edema may also involve the insula, and less commonly the cingulate regions. Contrast enhancement variably occurs in some. Chronic sequelae include atrophy of the medial temporal lobes, which may appear similar to mesial temporal sclerosis.

BACTERIAL MENINGITIS

Bacterial meningitis typically causes leptomeningeal enhancement that is noted on postcontrast
imaging (Figure 6), but this can be quite difficult to visualize on postcontrast CT unless severe. Pre- or postcontrast CT usually delineates only severe, secondary findings such as hydrocephalus, sulcal effacement, or multifocal regions of cortical edema (sometimes cytotoxic). Thus, pre- and postcontrast FLAIR MRI has perhaps greater sensitivity than pre- and postcontrast T1-weighted imaging (T1WI) in detecting meningitis; on precontrast images, FLAIR demonstrates bright sulcal signal, which becomes more pronounced on postcontrast FLAIR (which depicts the enhancement greater than postcontrast T1WI, which is usually also positive). However, one should exercise caution when noting bright sulcal signal on FLAIR, as leptomeningeal carcinomatosis, subarachnoid hemorrhage, unabsorbed gadolinium (such as from a recent MRI in a patient with renal failure), and 100% supplemental oxygen may also cause bright signal on FLAIR.

Figure 2. Acute lobar intraparenchymal hemorrhage (IPH). (A) A 43-year-old man with a seizure was found to have a hyperdense acute IPH within the left middle and superior temporal gyri (arrows) on noncontrast CT. (B) On a 1.5-T MRI, the IPH was isointense to gray matter on noncontrast T1-weighted images, while (C) being mostly dark on T2*-weighted images, consistent with the acute nature of the hematoma.

Figure 3. Acute subdural hemorrhage (SDH). (A) A 54-year-old woman with new seizures had an acute SDH (white arrows) causing a moderate degree of mass effect on noncontrast CT. The patient’s symptoms improved without surgery, so the patient was followed clinically. However, the patient presented 2 weeks later with altered mental status, and the follow-up (B) axial and (C) coronal images at that time demonstrated that the mass effect had become severe, resulting in uncal herniation (C, red arrow).
Regarding abscesses and subdural empyemas, postcontrast CT, T1WI, or FLAIR may note the rim of contrast enhancement from the inflamed surrounding parenchymal tissue or dura, respectively (Figure 7). However, the most sensitive sequence for detecting cerebral abscess or empyema is DWI, in which the highly viscous fluid has reduced diffusion (bright on DWI, dark on apparent diffusion coefficient [ADC] map).

**VIRAL ENCEPHALITIS**

Acute viral encephalitides in general are highly associated with acute seizures. The appearance and regional involvement by viral encephalitis varies with the causative virus, which is better imaged by MRI as it better localizes the regional edema (thus potentially enabling identification of the causative agent) compared to CT, which may demonstrate only nonspecific edema or swelling. Some of the more common viral causes of encephalitis are covered below.
Herpes encephalitis typically exhibits bilateral temporal lobe edema (bright on FLAIR and T2-weighted imaging [T2WI]), particularly in the medial temporal lobe (Figure 8), which may manifest as reduced diffusivity (bright on DWI) and variable degrees of contrast enhancement (more commonly not present). Varicella zoster virus encephalitis is an uncommon source of infection in immunocompetent or immunocompromised patients, and may variably present with basal ganglial, thalamic, and even cerebellar MRI findings in the immunocompetent patient, with variable generalized white matter abnormalities in immunocompromised patients. Subacute sclerosing panencephalitis may be a chronic infection that is insidious, occurring in those infected by measles virus. The appearance varies from cortical/subcortical involvement, diffuse white matter abnormalities, and/or basal ganglia and thalamic involvement; this disease is rarely acute and rapidly progressive. Rubella encephalitis
is also uncommon, and may present with nonspecific white matter cerebral abnormalities or spinal cord involvement. Influenza encephalitis involves the cortex and subjacent white matter on T2WI and FLAIR, which may also be manifested as bright signal (reduced) on DWI. H1N1 encephalitis typically appears normal on cranial MRI, although more severe necrotizing or lobar forms may rarely occur with rapid clinical progression. Japanese encephalitis typically is manifested as T2- and FLAIR-bright basal ganglia and/or thalamic involvement, also with variably reduced diffusivity and enhancement. West Nile virus encephalitis can appear somewhat similar to and in a similar regional distribution as Japanese encephalitis, but in West Nile the abnormalities can be a bit more patchy (less confluent) and involve not only the basal ganglia, but also the insula and immediate periventricular white matter (T2- and FLAIR-bright, usually without reduced diffusivity on DWI). Less common is equine encephalitis, which can have a similar appearance of basal ganglia and thalamic involvement. Cranial MRI usually appears normal in dengue virus. In HIV encephalitis, there is typically chronic atrophy and sulcal enlargement that can markedly progress over time, usually accompanied by diffuse and confluent mild, “hazy” white matter hyperintensity on FLAIR and DWI. Cytomegalovirus encephalitis (also called human herpes virus 5 [HHV-5]), typically occurs in immunocompromised patients and presents with increased T2- and FLAIR signal throughout the white matter, with variably bright signal on DWI and contrast enhancement; rarely, this may occur in an immunocompetent patient and present with bilateral thalamic or basal ganglial involvement. Progressive multifocal leukoencephalopathy also occurs in immunocompromised hosts (from JC virus), and can manifest as one or more white matter lesions that begin as subcortical and focal and are bright on FLAIR/T2WI; these may variably demonstrate reduced diffusivity (bright on DWI) and contrast enhancement, causing such lesions to overlap in appearance with demyelinating lesions or even primary brain tumors if the clinical history is not already known. Parvovirus (B19) may also infect immunocompromised patients, with resultant multifocal cerebritis or cerebellitis. Epstein-Barr virus encephalitis may occur in immunocompromised or immunocompetent hosts, with variably bright signal in the periventricular white matter on FLAIR and DWI that may reverse. Nipah virus is less common, and may demonstrate periventricular white matter lesions or confluent lobar lesions with bright

Figure 8. Herpes encephalitis. In a 48-year-old woman, there is (A) moderate-severe edema within the right temporal lobe on FLAIR, with (B) reduced diffusivity on diffusion-weighted images within the medial temporal lobe, (C) lacking contrast enhancement on postcontrast T1-weighted images. The affected parenchyma in such cases variably enhances with contrast.
signal on T2WI/FLAIR and variable enhancement. Notably, pituitary hemorrhage and hypofunction may occasionally occur from hantavirus or hemorrhagic fever. Numerous other viral forms of encephalitis may occur, which are too lengthy to be described here, and many of which are described on MRI by scattered case reports.

**LUPUS CEREBRITIS**

Lupus cerebritis is uncommon, but may consist of “patchy” cortical and subcortical edema on FLAIR/T2WI with variable enhancement. What seems to be more common is that lupus can predispose to the onset of posterior reversible encephalopathy syndrome (PRES). Periventricular white matter lesions may also rarely occur in lupus and other autoimmune encephalitides, and these abnormalities may present acutely with white matter abnormalities diffusely on FLAIR and DWI that can impressively reverse and even resolve following therapy.

**POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME**

PRES is a clinicoradiologic syndrome in which the imaging may antedate the clinical diagnosis or vice versa. The edema typically involves the cortex first in early or milder cases, and extends centripetally towards the ventricles with increasing severity. Hence, subtle cases may be difficult to visualize on CT and may only be detected by FLAIR MRI (Figure 9). Thus, FLAIR MRI is the most sensitive sequence to evaluate this disorder where the cortex and subcortical white matter are involved in more subtle cases. Diffusion-weighted images have regions of cytotoxic “reduced diffusion” (usually punctate or small, focal and gyral) in just under 20% of cases. Single or multiple intracerebral hemorrhages with dimensions larger than 2 mm have been estimated to occur in about 20% of PRES cases. Interestingly, punctate microhemorrhages may occur as sequela in up to 50% of cases, and these microhemorrhages persist chronically; however, the propensity for these microhemorrhages to cause chronic epilepsy has not yet been ascertained.

Contrast enhancement may occur in 30% to 40% of cases (usually leptomeningeal or focal cortical), but this has been shown to be of little clinical import, even if the appearance is quite pronounced.

**OTHER WHITE MATTER ABNORMALITIES**

Other acute white matter MRI abnormalities are sometimes encountered during epilepsy or seizure evaluations. A focal signal alteration in the splenium of the corpus callosum has been presumed to represent demyelination and typically is reversible. This “reversible splenial lesion syndrome” is most often associated with acute withdrawal of antiseizure medications in chronic epilepsy and with acute encephalitis or other acute encephalopathies. Central pontine myelinolysis (CPM) and other osmotic demyelinating syndromes are often associated with acute symptomatic seizures, but the seizures usually are accounted for by hyponatremia or other demyelinating insults; while highly characteristic MRI findings occur in CPM, these findings are of limited direct relevance to the seizures. Acute toxic leukoencephalopathy is less often associated with seizures than is PRES.

**CAUSATIVE LESIONS IN STATUS EPILEPTICUS**

Brain imaging is necessary to diagnose causative lesions in generalized convulsive and nonconvulsive status epilepticus (GCSE and NCSE), and in general the lesions detected will be those associated with acute symptomatic seizures or with chronic epilepsy (as reviewed in the Part 3 article). Reversible signal abnormalities in the hippocampus and neocortex can be caused by GCSE,
NCSE, and acute repetitive seizures, however. It is important to recognize such CT and MRI alterations, since these should not be biopsied or resected, but only followed out to full resolution with serial imaging. Focal and multifocal T2 signal increases in white matter predominate over gray matter T2 hyperintensities on early post-status epilepticus MRI, presumably due to seizure-related neuroglial injury that induces vasogenic edema before cytotoxic edema. Subtle extracellular fluid accumulation due to frequent or intense seizures is better detected with DWI, which can be used to map out areas of likely ictal onset and propagation.

**STRUCTURAL IMAGING APPLICATIONS IN THERAPY OF CHRONIC EPILEPSY**

Structural imaging abnormalities are major components of epilepsy syndromic diagnosis, which leads to effective or at least optimized medication selection. When epilepsy is refractory, the detection of causative or associated structural lesions is
Structural Brain Imaging in Acute Seizures

Essential in presurgical planning. Despite advances in structural brain imaging, “MR-negative” refractory epilepsy patients are often encountered, and in these cases functional imaging and intracranial electroencephalography (EEG) are often used. Brain MRI and CT are also essential in determining coordinates for stereotaxic placement of intracranial electrodes for seizure recording, and once the electrodes are placed, MRI and CT are highly useful to confirm their actual locations as an essential step in the electrophysiological diagnosis and to exclude iatrogenic hemorrhages. Online imaging-based anatomical correlation with the operative field during resection can assist in evaluating the locations of critical landmarks and the completeness of lesionectomy. Following epilepsy surgery, brain MRI and CT are used to screen for acute complications, and later they are especially useful in identifying surgical failures that can be turned into successes with additional limited resection (eg, when small areas of residual hippocampus or remaining focal cortical dysplasia appear to be the site of ictal onset). These applications of structural imaging will be considered further in this series in subsequent articles that review therapeutics.

INTERICTAL FDG-PET

Interictal 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is the most commonly employed functional imaging technique in evaluation of refractory partial epilepsies. This is partly explained by the greater ease of obtaining technically satisfactory FDG injection interictally, as compared with difficulties in obtaining ictal injections for SPECT studies. Intense increase in the regional cerebral metabolic rate for glucose (CMRGlc) is observed during partial-onset seizures in both experimental and clinical settings. The more relevant observation regarding regional CMRGlc is that focal areas of interictal decrease are highly associated with the ictal onset zone in refractory partial epilepsies. Ictal FDG-PET studies cannot be quantified because glucose metabolism is not at steady-state. Interictal FDG-PET is widely available, mainly because of its broad application for detecting subtle tumors of various types in oncology. While PET-CT is standard due to its oncological applications, the CT component is of limited value in epilepsy imaging; PET-CT images must be adapted to avoid obscuration of the glucose metabolic maps (Figure 10).

INTERICTAL FDG-PET IN MESIAL TEMPORAL LOBE EPILEPSY

In adults and children with refractory mesial temporal lobe epilepsy (TLE), interictal FDG-PET usually demonstrates hypometabolism of one temporal lobe or bilateral temporal hypometabolism with more severe hypometabolism of one temporal lobe. Qualitative visual analysis of FDG scans obtained with high-performance tomography currently detects unilateral (or bilateral but asymmetric) temporal lobe hypometabolism in over 70% of refractory TLE patients. Higher-resolution tomographic systems produce a higher detection rate for hypometabolism and greater concordance in scan interpretation in qualitative interpretation of FDG imaging in localization-related epilepsies. With quantitative analysis, detection of significant temporal hypometabolism may reach or exceed 90% in this group. Temporal lobe hypometabolism usually extends over the mesial and lateral portions of an interictally dysfunctional temporal lobe on FDG scans in mesial TLE (Figures 11, 12, 13, 14, 15). Regional hypometabolism in mesial TLE typically is diffuse, with graded demarcations from adjacent...
areas of normal metabolism and with a relatively large area of hypometabolism. Even in the presence of a temporal lobe foreign-tissue lesion, patients with refractory mesial temporal seizures usually have widespread temporal lobe hypometabolism, rather than focal hypometabolism restricted to the site of the lesion. The lateral temporal hypometabolism often appears more severe than the mesial temporal hypometabolism of an affected temporal lobe on qualitative scan interpretation. Two quantitative investigations also demonstrated that hypometabolism of lateral temporal areas was more severe than hypometabolism of mesial temporal areas in many mesial TLE patients.50,62 Using clinical PET systems, partial-volume averaging of severe hypometabolism in the epileptogenic amygdala-hippocampus together with less depressed metabolism of adjacent basal temporal areas may cause the mesial temporal areas to appear less severely hypometabolic than they actually are. Normal interictal metabolism also occurs in refractory mesial TLE, but normal FDG scans are more common in nonrefractory than in refractory mesial TLE.

Many TLE patients have unilateral frontal, parietal, thalamic, or basal ganglial hypometabolism ipsilateral to temporal hypometabolism, but occipital hypometabolism is rare in mesial TLE.47,50,54 The temporal hypometabolism is nearly always more severe than any extratemporal hypometabolism. The cortical hypometabolic area typically is contiguous across its entire temporal and extratemporal extent. Bilateral cerebellar hypometabolism is common. Thus, interictal FDG-PET in refractory mesial TLE usually reveals unilateral diffuse regional hypometabolism of one mesial-lateral temporal area, with or without ipsilateral extratemporal cortical hypometabolism or contralateral temporal hypometabolism; ipsilateral extratemporal and contralateral temporal hypometabolism appear...
less severe than the temporal lobe hypometabolism. On comparing the anatomical distributions of ictal hyperperfusion (using SPECT) and interictal glucose hypometabolism (using FDG-PET) within individual TLE patients, it is evident that many TLE patients have an identical or highly similar distribution of ictal hyperperfusion/interictal hypometabolism that predominates in the temporal lobe and thalamus ipsilateral to the epileptogenic site (including but extending beyond the electrographic ictal onset zone), often with less severe involvement of ipsilateral frontoparietal and basal ganglial sites and contralateral temporal cortex. One exception is the occipital hyperperfusion often observed in the absence of occipital hypometabolism in TLE.

The pathophysiological basis of regional hypometabolism imaged with FDG interictally in TLE currently is unclear. Ablative structural lesions must contribute to localized decreases in glucose metabolism. Nonetheless, it has been recognized for some time that the volume of hypometabolism is greater than the volume of associated struc-

Figure 11. Interictal FDG-PET images of a patient with mesial temporal lobe epilepsy. These transaxially oriented images show anterior hippocampal hypometabolism (arrowhead), which is more severe than reduction in FDG activity in the adjacent inferior-lateral temporal regions. No extratemporal abnormalities are evident. The patient's brain MRI was normal. Mild hippocampal sclerosis was present in tissue resected on the side of hypometabolism and extracranially recorded electroencephalography ictal onsets. Seizures ceased after resection.

Figure 12. Interictal FDG-PET images of a patient with mesial temporal lobe epilepsy. These coronally oriented images were reconstructed from the same FDG data as the images shown in Figure 11. The mesial greater than lateral temporal hypometabolism is evident (at arrowhead and on adjacent planes). On each row, the coronal images are arranged with the most anterior plane to the left and 4 mm spacing. Subject left is displayed on image right.
Neuronal loss and diaschisis were considered the causes of the anatomically distributed interictal hypometabolism in TLE patients with hippocampal sclerosis. This hypothesis was refuted by a study of quantified preoperative FDG-PET in patients whose resected temporal tissue underwent quantitative neuronal volumetric densitometry. The diagnostically robust patterns of interictal glucose hypometabolism are not fully explained by macrostructural and microstructural alterations in TLE.

Focal mesial temporal hypermetabolism sometimes occurs interictally in children with mesial TLE, but rarely occurs in adults with localization-related epilepsies. Continuous or repetitive focal mesial temporal seizures that are subclinical and not detectable with scalp electrodes may cause “interictal” deep temporal hypermetabolism. Alternatively,
Ictal or peri-ictal (mixed ictal-postictal-interictal) FDG scans are difficult to obtain and to interpret. True ictal imaging with FDG is restricted to status epilepticus, due to the relatively poor temporal resolution of the FDG method. Occurrence of a single complex partial seizure during the FDG uptake period may be associated with the usual interictal findings of unilateral temporal hypometabolism. In one reported case, a partial seizure occurred about 2 minutes after FDG injection and the scan appeared normal; the same patient later had marked hypometabolism of the epileptogenic temporal lobe on an interictal FDG scan.\textsuperscript{48} Presumably, ictal hypermetabolism was averaged with interictal-postictal hypometabolism over the temporal lobe to cause “normalization” of FDG activity on the peri-ictal scan. In another case, a TLE patient had repeated complex partial seizures following FDG injection, and the scan showed hypermetabolism over the epileptogenic temporal lobe, with ipsilateral frontal and thalamic metabolic increases.\textsuperscript{33,65} Alterations on ictal and peri-ictal FDG images likely reflect dysfunctions in areas of ictal propagation and interictal and postictal dysfunction in these areas. It is difficult or impossible to sort out the relative contributions of these various dysfunctions to a single set of FDG images.

**INTERICTAL FDG-PET IN OTHER LOCALIZATION-RELATED EPILEPSIES**

Interictal FDG-PET often demonstrates a region of pathologic hypometabolism in adults and children with refractory partial seizures of extratemporal origin or neocortical (extralimbic) temporal origin (Figure 16).\textsuperscript{4,45,46,48,54,56,66–70} In patients with a single neocortical site of ictal onset, interictal FDG-PET usually demonstrates a single region of hypometabolism, but normal metabolism also is frequently observed. Compared with nonlesional limbic TLE, nonlesional neocortical epilepsies are much more likely to have normal interictal FDG-PET studies.\textsuperscript{66,67} Interictal focal neocortical areas of hypermetabolism may occur in early childhood epilepsies,\textsuperscript{63} but have not been reported in adults. In many lesional neocortical epilepsies, the hypometabolic region is small, sharply circumscribed, and co-localized with a focal structural lesion detected...
with MRI; a similar relationship of “matching” focal PET hypometabolism and focal MRI lesion rarely is observed in limbic TLE. Many individuals with lesional or nonlesional neocortical localization-related epilepsies have a more widespread hypometabolic zone, which has graded transitions from areas of severe hypometabolism to areas of normal metabolism, similar to patterns of hypometabolism in limbic TLE. When associated with a lesion, a diffuse hypometabolic area of neocortex often is much larger than any associated structural imaging abnormality and than any histopathological lesion, as also is observed in limbic TLE. In the absence of a structural lesion on MRI, the volume of diffuse regional hypometabolism sometimes is fairly small in neocortical epilepsies. Larger areas of hypometabolism often include mesial temporal, thalamic, and basal ganglial hypometabolism ipsilateral to the neocortical site of hypometabolism. Hypometabolism over an entire hemisphere is rare in unilateral neocortical epilepsies, as is symmetric bilateral hypometabolism. The degree of hypometabolism usually varies across a region of diffuse hypometabolism. The zone of most severe hypometabolism, excluding the site of a foreign-tissue lesion, usually contains the electrophysiologically defined ictal onset zone.

Ictal or peri-ictal FDG imaging during simple partial seizures of neocortical frontal origin demonstrates patterns of increased and decreased FDG uptake, which likely reflect neuronal activity at the site of ictal onset, in areas of ictal spread, and in regions involved in postictal depression. Epilepsia partialis continua can be associated with a small volume of cortical hypermetabolism or hypometabolism when the ictal discharge remains limited, or more diffuse unilateral cortical and thalamic hypermetabolism or hypometabolism when intrahemispheric spread occurs. In one patient with epilepsy partialis continua manifested as left arm and leg clonus, right frontal hypermetabolism and other bilateral regions of hypermetabolism were present. In other cases of epilepsy partialis continua, FDG scans have revealed focal frontal hypermetabolism with ipsilateral thalamic or contralateral cerebellar hypermetabolism, or widespread hypometabolism without detectable areas of hypermetabolism.

INTERICTAL FDG-PET IN GENERALIZED EPILEPSIES

Interictal FDG studies are normal in idiopathic generalized epilepsies. Some patients with
symptomatic generalized epilepsies and some with localization-related epilepsies also have normal interictal FDG imaging,\(^50,76\) so the finding of normal interictal cerebral glucose metabolism is not useful in syndromic classification.

Patients with West syndrome have been extensively studied with FDG imaging in both research applications and presurgical evaluation. Unilateral cortical metabolic dysfunctions (hypo- or hypermetabolism) are relatively common in West syndrome.\(^77–80\) Bitemporal hypometabolism is less common, occurring in approximately 15% of infants with spasms in Chugani’s series. In this series, bitemporal hypometabolism was never associated with a single predominant zone of structural imaging or electrophysiological abnormality, so surgery was never performed; most of these infants later developed autism.\(^80\) (Bitemporal hypometabolism also has been reported in autistic children who had partial status epilepticus early in life;\(^81\) but these children had evidence of hippocampal sclerosis on MRI.) By contrast, approximately 20% of infants with refractory spasms had FDG studies showing unilateral cortical regions of metabolic dysfunction (Figure 17); those who underwent unilateral cortical resection, which usually included large volumes of cortex, often had cessation of seizures and normal or near-normal cognitive development.\(^61,82\)

Many infants with West syndrome have both unilateral cortical metabolic dysfunction and bilateral lenticular and brainstem metabolic dysfunction.\(^78\) Chugani has hypothesized that infantile spasms begin with a focal cortical abnormality that induces brainstem activities that are projected symmetrically to the basal ganglia and spinal cord.\(^78\) This theory is consistent with the observations that infantile spasms are generalized from onset, and that unilateral cortical resection can result in cessation of the spasms.\(^77\) Such patients often have cortical dysplasias in resected tissue, and in some of these cases brain MRI did not detect the malformation.\(^63,83\) Chugani has suggested that in infants the normal absence of myelination of subcortical white matter may render MRI less sensitive in detecting subtle neuronal heterotopia and other dysplastic features, compared with the high sensitivity of MRI for dysplasias in children and adults with completed myelination.

Patients with the Lennox-Gastaut syndrome usually have multiple regions of bilateral cortical hypometabolism interictally on FDG scans (Figure 18),
but sometimes have predominantly unilateral hypometabolism when patients with structural lesions are included. When only Lennox-Gastaut patients with no lateralizing findings on neurological examination and with normal cranial CT scans were imaged with FDG interictally, most patients had symmetric generalized cortical and thalamic hypometabolism, although a few had symmetric generalized cortical hypermetabolism. A series of 32 children with “cryptogenic epileptic encephalopathies,” which presumably included mainly children with symptomatic generalized epilepsies, demonstrated generalized metabolic dysfunction in most cases (usually hypometabolism, but hypermetabolism in some), regional metabolic dysfunction in some cases, and normal metabolism in only 2 cases. The FDG scans in this series detected thalamic hypometabolism in 90% of cases, which was usually bilateral, but thalamic metabolism was lower on the side of more severe cortical hypometabolism.

Patients with electrical status of slow-wave sleep typically have unilateral focal or multifocal sites of hypermetabolism during sleep, with more nearly normal cerebral glucose metabolism during waking. The sites of metabolic dysfunction mainly were found in association cortex. This childhood syndrome of continuous generalized spike-and-wave discharges during slow-wave sleep, usually with dementia or progressive aphasia, and with clinically evident epileptic seizures thus provides another example of a symptomatic generalized epilepsy in which generalized EEG phenomena are associated with focal or multifocal cortical metabolic dysfunction.

**INTERICTAL AND ICTAL CEREBRAL BLOOD FLOW SPECT**

Successful ictal SPECT studies require established protocols for very rapid identification of
seizure onset as well as rapid and safe injection of radiopharmaceuticals by appropriate staff. In some centers, nurses or even physician-trainees are assigned to observe patients continuously during periods with a high probability of seizure activity, such as occurs after medication tapering for inpatient video-EEG monitoring, in order to inject SPECT tracers during EEG seizure discharges. A practical alternative is to train and certify EEG technologists in radiopharmaceutical administration, since EEG technologists can be present to perform other duties at the site of video-EEG monitoring and also are highly skilled in rapid detection of seizure onset. Ictal SPECT protocols with specially certified EEG technologists have proved successful. Relevant aspects of SPECT methodology have been reviewed in detail.

The temporal relationships of radioligand injection to ictal EEG discharges and ictal semiology are of paramount importance in analysis of cerebral perfusion patterns. Inaccurate interpretation of delayed postictal injection as representing injection during the ictus may cause false lateralization of interhemispheric asymmetries of cerebral blood flow (CBF) due to the “postictal switch” phenomenon, as discussed below. Both interictal and ictal CBF images must be compared in the same patient, as unrecognized interictal abnormalities might lead to false localization of ictal hyperperfusion if it is wrongly assumed that ictal perfusion patterns are changed from a normal interictal CBF distribution. The interictal and ictal image acquisitions can be performed hours or days apart. Acquisition of ictal and interictal SPECT usually is performed during inpatient video-EEG monitoring, which provides both behavioral observations and continuous EEG recording.

Subtraction ictal SPECT coregistered to MRI (SISCOM) techniques were developed after more than a decade of experience with qualitative visual comparison of ictal and interictal SPECT scans. A considerable increase in sensitivity and specificity is afforded by coregistration and subtraction of ictal and interictal SPECT images, followed by superimposition on the individual’s MRI scan and statistical analysis of CBF differences. The kinetics of [Tc-99m]ECD (ethyl cysteinate diethylester) may be superior to those of unstabilized [Tc-99m]HMPAO (hexamethyl propylene amine oxime) in permitting radioligand injection earlier during the seizure (Figure 19) and therefore may increase the specificity of ictal SPECT findings. In general, stabilized HMPAO and ECD have been considered as equivalent for ictal SPECT, although one study found that the dynamic range of ictal hyperperfusion on stabilized HMPAO images was greater than that afforded by ECD.

Intense increases in regional cerebral blood flow (rCBF) and glucose metabolism are hallmarks of partial-onset seizures. Single seizures usually last for less than 90 seconds (and most often are considerably briefer than that) and occur less than once per day (and often far less than that) for most individuals with epilepsy. In the setting of an epilepsy monitoring unit, with antiepileptic drugs reduced or discontinued, injection of [99mTc]HMPAO or [99mTc]ECD can be accomplished during or within seconds following termination of a complex partial seizure. Peri-ictal SPECT imaging of CBF has excellent accuracy in determining the region of ictal onset and predominant propagation in refractory partial epilepsies, both in adults and in children. When the radiopharmaceutical is injected during the electrographic seizure, over 90% of patients with unilateral TLE have regional hyperperfusion over mesial and lateral portions of the temporal lobe of ictal onset. Ictal hyperperfusion also frequently extends to contiguous areas...
of ipsilateral extratemporal cortex and to ipsilateral basal ganglia and thalamus, although recent studies have noted frequent occurrence of ictal hyperperfusion of ipsilateral frontoparietal areas and CBF changes in bilateral occipital regions.\textsuperscript{103,110–112} Many patients have ictal hyperperfusion of the cerebellum contralateral to the cerebral site of ictal onset, although ipsilateral or bilateral cerebellar hyperperfusion also may occur.\textsuperscript{113} Bilateral temporal hyperperfusion occurs in some ictal SPECT studies in TLE,\textsuperscript{91} but the epileptogenic temporal lobe has greater CBF increase from the interictal to the ictal scan than the contralateral lobe. Resolution of ictal and early postictal hyperperfusion occurs at different rates in different brain regions. Ictal HMPAO SPECT also is useful in determining the region of ictal onset and predominant propagation in extratemporal partial epilepsies.\textsuperscript{102,106}

Ictal SPECT studies can clarify the anatomical substrates of ictal semiology. Partial seizures that cause greater impairment of consciousness (without causing a full generalized tonic-clonic seizure) are more likely to show hyperperfusion of the thalami and midbrain, in addition to cortical hyperperfusion, than are simple partial seizures.\textsuperscript{110,114} Greater degrees of ictal impairment of consciousness and motor phenomena are associated with greater propagation of CBF increases to the contralateral hemisphere.\textsuperscript{111} Newton and colleagues examined the ictal hemidystonia that often occurs late in complex partial seizures in TLE.\textsuperscript{104} They demonstrated unilateral basal ganglia hyperper-
fusion during seizures with hemidystonia of the opposite limbs, which was consistently ipsilateral to the temporal lobe of ictal onset, but found no basal ganglia CBF changes during complex partial seizures without dystonia. In the rare epileptic syndrome of hypothalamic hamartoma with gelastic seizures, a complex partial seizure was associated with hypothalamic hyperperfusion in the absence of temporal lobe or other cortical CBF changes, thus supporting other lines of evidence that focal seizures can originate in the hypothalamus. It is well known that ictal semiology can be altered by changes in antiepileptic drug regimens. A further question that might be addressed with ictal SPECT is how different antiepileptic drugs affect ictal onset-propagation CBF distributions.

Peri-ictal SPECT studies of TLE have shown a characteristic evolution in regional CBF, as the region of ictal hyperperfusion declines to severe hypoperfusion for several minutes postictally, then within about 20 minutes perfusion rises back to a milder degree of interictal hypoperfusion. This phenomenon has been called the “postictal switch.” Resolution of ictal and early postictal hyperperfusion and of later postictally enhanced hypoperfusion occurs at different rates in different brain regions. This postictal switch phenomenon is extremely important to recognize in clinical applications of ictal SPECT because false lateralization of the ictal onset zone might occur if a “switched” postictal CBF asymmetry is misinterpreted as representing an ictal CBF asymmetry.

Generally, with partial seizures the ictal hyperperfusion persists into the postictal state. The ictal-interictal SPECT subtraction can be reversed to provide data that show areas of relative hypoperfusion. This is important if the SPECT injection was in the postictal state, which is particularly likely in brief partial seizures. This hypoperfusion map occasionally provides useful localizing information when combined with knowledge of the video-EEG data and injection timing.

Other Functional Imaging Modalities

A number of other functional imaging modalities have shown consistent abnormalities that may be of diagnostic utility in epilepsy evaluations, particularly in planning epilepsy surgery. Chief among these other modalities are MRS with proton and phosphorus spectra, language- and memory-activation functional MRI, and PET with central benzodiazepine receptor mapping and serotonergic systems mapping. Although many epilepsy centers have begun to use these techniques clinically, the clinical applications of these modalities have not been standardized across large numbers of epilepsy centers.

Board Review Questions

Test your knowledge of this topic. Go to www.turner-white.com and select Epilepsy from the drop-down menu of specialties.

References

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