Neuroimaging in the Evaluation of Epilepsy

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Abstract

Keywords

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Neuroimaging has provided extraordinary insight into the pathologic substrate of epilepsy. The excellent spatial resolution and soft tissue contrast of magnetic resonance imaging (MRI) allows identification of a substantial number of pathologies including hippocampal sclerosis, malformations of cortical development, low grade tumors, and vascular abnormalities, among others. Complementary imaging modalities such as positron emission tomography, single photon emission computed tomography, and magnetoencephalography can be diagnostically helpful as well. Identification of a pathologic substrate is particularly important in patients with medically refractory epilepsy who are undergoing evaluation for surgery, and essential in determining the likelihood of seizure freedom after surgical intervention. This article reviews current and emerging neuroimaging techniques in the field of epilepsy.

One of the greatest advances in the investigation of epilepsy in the 20th century was the introduction of brain imaging. Neuroimaging has provided an extraordinary insight into the pathologic substrate of epilepsy, which is essential in determining probable course of disease, appropriate treatment, surgical candidacy, and likelihood of seizure freedom after surgical intervention. The invention and development of the electroencephalogram (EEG) predated computer tomography (CT) and magnetic resonance imaging (MRI) by decades, and as a consequence, the classification of seizures and epilepsy has been based on electroclinical features, rather than etiology or anatomic findings.¹ However, as the dynamic field of neuroimaging evolves, the paradigms for the classification of epilepsy progressively shift toward an anatomic and functional approach. Recognizing this trend, this article focuses on the neuroradiologic findings of different pathologic substrates for epilepsy.

Imaging Modalities in Epilepsy

Although the routine use of CT for the evaluation of epileptic patients has decreased with availability of MRI, given its accessibility and lower cost, it is still used in emergency scenarios and when high-resolution imaging cannot be obtained. CT can

accurately detect hemorrhages, gross structural malformations, large tumors, and calcified lesions. In 1976, shortly after the development of this technique, Gastaut reported a proportion of 34–51% cerebral lesions in epileptic patients.² A comparison of early versions of T2-weighted spin-echo MRI and contrast-enhanced CT in patients undergoing surgical evaluation for refractory partial epilepsy showed that these modalities detected 83% and 58% of the causative lesions, respectively.³

Brain MRI not only has higher sensitivity than CT, but also better spatial resolution and soft tissue contrast. In addition, it allows multiple plane imaging as well as functional cerebral assessment through different techniques. All these characteristics make MRI the primary imaging modality for the evaluation of patients with epilepsy. MRI with a dedicated epilepsy protocol increases even more the frequency with which epileptogenic lesions are identified.⁴ Although protocols vary from institution to institution, most include axial and coronal oblique T2-weighted fast spin echo (FSE) and fluid attenuated inversion recovery (FLAIR) sequences, as well as coronal magnetization-prepared rapid acquisition gradient echo (MPRAGE) and / or spoiled gradient recalled echo (SPGR) volumetric dataset.

Contrast enhanced and gradient echo (GRE) images and single voxel spectroscopy are also included in some protocols

because these are useful in the identification of specific pathologies such as tumors and sequelae of traumatic brain injury (TBI). There are newer advanced techniques that can be used to further delineate the epileptogenic substrate and its relationship with surrounding tissue, such as diffusion tensor imaging (DTI), which reveals white matter tracts with great precision. Moreover, functional MRI (fMRI) has been used for the identification of eloquent cortex, especially when related to language, in patients undergoing presurgical evaluation.

Although MRI provides invaluable information for the identification of the anatomic substrate of epilepsy, other complementary neuroimaging modalities are required in complex cases and when planning for surgical resection of the epileptogenic focus. Positron emission tomography (PET), for example, makes use of glucose metabolism (^{18}F -fluorodeoxyglucose [^{18}F -FDG]) as an indirect measure of neuronal function. An epileptogenic focus typically appears as an area of hypometabolism on interictal scans and an area of hypermetabolism on ictal scans. However, its ability to image cerebral metabolism is limited to the interictal state due to the long radiotracer uptake time (30–45 minutes) that is significantly longer than the average seizure duration.⁵

Single photon emission computed tomography (SPECT) entails the use of $^{99\text{m}}\text{Tc}$ -HMPAO (technetium-99 hexamethylpropylene amine oxime) or $^{99\text{m}}\text{Tc}$ -ECD (technetium-99m-ethylcysteinate diethylester) as substrate to assess regional cerebral blood flow changes during both the ictal and interictal periods. The epileptogenic focus typically appears as an area of hypoperfusion in the interictal state and hyperperfusion in the ictal state. Interictal SPECT has low sensitivity, but SPECT perfusion difference (ictal–interictal) is believed to have higher sensitivity and specificity than any other noninvasive localizing criterion.⁶ However, ictal imaging is technically challenging as it requires dedicated personnel waiting at the bedside to accomplish the tracer injection within the initial few seconds after seizure onset.

Magnetoencephalography (MEG) is another imaging modality utilized for the identification of the source(s) of epilep-

tiform activity during presurgical evaluation. It is especially useful in cases where primary modalities, including ictal EEG and MRI, are not clearly localizing. It is also used for the mapping of presurgical eloquent cortex, such as in the lateralization and regional localization of language.^{7,8} Although EEG measures electrical signals that originate from volume-conducted extracellular activity, MEG detects electromagnetic neural activity that arises from intracellular postsynaptic currents.^{9,10} MEG is most sensitive to tangentially oriented cortical sources, and it has excellent temporal and good spatial resolution.^{11,12} The magnetic dipoles generated by MEG are then superimposed on structural MR images, creating magnetic source imaging (MSI). This technique provides nonredundant clinical information in about one-third of the epilepsy cases undergoing presurgical evaluation.¹³ Unfortunately, its use in the localization of epileptogenic activity is limited to the interictal state due to physical constraints such as the size of the machine and the need for a magnetically shielded room.

Hippocampal Sclerosis

The syndrome of mesial temporal lobe epilepsy (MTLE) is the most common form of symptomatic localization related epilepsy.¹⁴ The associated histopathologic substrate is usually hippocampal sclerosis (HS),^{15,16} which can be reliably detected by MRI (**► Fig. 1**). Optimal imaging of the hippocampus requires orthogonal axial and coronal sequences, with axial images in a plane along the long axis of the hippocampus. Classic findings of hippocampal sclerosis are atrophy of the hippocampal gray matter, best shown on inversion recovery sequences, and increased hippocampal signal on T2-weighted images (T2WI). A series of 81 patients that underwent therapeutic temporal lobectomy, with pathologic findings available in all patients, demonstrated that MRI can detect HS with great sensitivity (93%) and specificity (86%).¹⁷ MRI evidence of hippocampal atrophy has been shown to have a positive predictive value of up to 86% for excellent

Fig. 1 Hippocampal sclerosis. A 31-year-old right-handed woman had frequent seizures consisting of staring and automatisms, then fist clenching, upper extremity posturing, and reduced level of consciousness. During events, electroencephalogram (EEG) showed rhythmic sharp waves centered over the right anterior temporal lobe electrodes. (A) Coronal T2-fluid attenuated inversion recovery magnetic resonance imaging (FLAIR MRI) showed abnormal hyperintensity in the right hippocampus. (B) Axial T2-FLAIR MRI with fat suppression confirmed abnormal hyperintensity in the right hippocampus. (C) Interictal ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG-PET) showed corresponding hypometabolism (darkness) in the right temporal lobe. (D) The patient underwent right anterior lobectomy, seen on axial T2-FLAIR MRI, with pathologic evidence of marked hippocampal neuronal loss and gliosis. The patient is seizure-free without anticonvulsant medications.

postoperative seizure control after anterior temporal lobectomy.¹⁸ However, in a minority of cases of HS, these qualitative radiologic findings are not present. This dilemma led to the development of quantitative volumetric hippocampal analysis. Volumetric methods correlate well with histopathologically confirmed hippocampal cell loss.¹⁹ Thus, reduced volume by quantitative analysis has been established as a surrogate marker for the presence and severity of hippocampal atrophy. In addition, hippocampal atrophy by MRI volumetry has been demonstrated to be 75% sensitive to, and 64% specific for, ipsilateral medial temporal lobe seizure onset as corroborated by intracranial EEG recordings.²⁰

Despite its known utility, hippocampal volumetry has been difficult to incorporate in clinical practice because of the time demands and the technical skills required. As a solution, investigators have substituted time-consuming manual techniques with automated software for generic quantitative morphometrics. Recent studies have shown that these automated techniques can also detect hippocampal asymmetry and lateralize hippocampal atrophy accurately.²¹ Other techniques, such as T2 relaxometry and magnetic resonance spectroscopy (MRS), have encountered the same practical difficulties than volumetric analysis and their use for the detection of HS has been limited mostly to investigational purposes. Hippocampal T2 relaxation time is prolonged ipsilateral to HS identified by visual inspection and volumetry.²² In MRS, comparison with control subjects has shown that the temporal lobe ipsilateral to the seizure focus (with evidence of HS on visual inspection) has a mean reduction in the NAA signal, increases in the Cr and Cho peaks, and an abnormally low NAA/Cho:Cr ratio.²³ However, in most cases, these metabolic abnormalities extend beyond the epileptogenic focus.²⁴

Often, in patients with MTLE, there are other MRI findings associated with those typical of HS. These include ipsilateral enlargement of the temporal horn, reduced size of the fornix and the mamillary body, loss of the normal interdigitations of the hippocampal head, hippocampal malrotation, and atrophy of the collateral white matter.^{25–27} However, their significance with regards to the diagnosis and prognosis of MTLE and HS is not well understood. With the advent of 7 Tesla (7T) MRI, there has been an increased focus in the study of these associated findings because ultrahigh field strength enables detailed evaluation of normal and abnormal hippocampal folding and rotation. Besides permitting the detection of selectively greater Ammon horn atrophy in MTLE with HS, this technique has also allowed the identification of a paucity of digitations of the hippocampal head as a deformity independent of hippocampal atrophy on the epileptogenic side of patients with MTLE.²⁸ Malrotation of the hippocampi is clearly visualized as well, but it has been detected in both MTLE and control subjects.²⁸ Studies with 7T MRI are limited to a small amount of subjects and further investigation of these findings is needed.

Patients can also present with dual pathology on MRI, including hippocampal atrophy in conjunction with an additional structural lesion.²⁹ The most common of such lesions are the malformations of cortical development, which have

been reported in up to 15% of patients with HS.³⁰ In addition, patients can present with bilateral, symmetric, or asymmetric hippocampal atrophy detected by visual or volumetric analysis.³¹ When this is the case, the epileptologist relies on the electroencephalographic documentation of the side of ictal onset and on other functional imaging modalities.

¹⁸F-FDG PET is routinely used in the presurgical evaluation of MTLE. Interictal studies show hypometabolism in a relatively wide area encompassing the temporal lobe of seizure onset, but the pathophysiology of this phenomenon is incompletely understood. In a meta-analysis by Spencer, the overall sensitivity of interictal FDG-PET to temporal lobe epilepsy as judged by EEG criteria was found to be 84% with a specificity of 86%.³² Furthermore, when pathologic groups were analyzed, PET measurement of metabolism had even higher sensitivity for HS. However, the extent of the hypometabolism does not correlate with the degree of cell loss or hippocampal atrophy.^{33,34} There seems to be an association between hypometabolism and uncontrolled seizures or medical refractoriness.^{35–37} In fact, ¹⁸F-FDG PET evidence of restricted temporal lobe hypometabolism, by visual inspection correlates with postoperative seizure control after anterior temporal lobectomy.³⁸ The absence of, or evidence of multilobar, hypometabolism is considered concerning when encountered during presurgical evaluation because it suggests worse surgical outcome.^{38,39} Some investigations have shown that compared with normal controls, more than 15% reduction in predominantly lateral temporal metabolism has the best correlation with seizure outcome (despite pathologic abnormalities in medial temporal areas),^{40–42} whereas others reported a correlation with hypometabolism of the medial temporal region.³⁸ Overall, the sensitivity of PET in MTLE is limited by the lack of localization within the temporal lobe. Despite its limitations, FDG PET is considered extremely useful in patients with medically intractable MRI negative TLE, in which the decision to surgically intervene is often taken on the basis of electrographic, metabolic, and neuropsychologic data.⁴³

Ictal SPECT is another functional imaging modality utilized in the presurgical evaluation of epilepsy. In patients with MTLE, it shows increased ictal cerebral perfusion in the medial and lateral temporal regions when the tracer injection is appropriately administered. In these patients, ictal SPECT is a very sensitive (90–93%), but not so specific (13–77%) diagnostic tool.³² Interpretation is difficult because it requires knowledge of seizure type, clinical activity, time of ictal injection in relation to seizure onset and MRI findings. From a practical point of view, in MTLE it adds little useful information beyond what is provided by EEG-video telemetry and structural MRI, especially when there is a lesion.⁴⁴ Hence, it usually does not alter the surgical decision and outcome for patients with HS. In fact, its use increases the length of hospital stay and subsequently, the costs and risks of video-EEG monitoring. The use of SPECT is usually reserved for the evaluation of intractable epilepsy of presumed extratemporal origin, and in some cases it is helpful in delineating the epileptogenic zone when planning for implantation of intracranial electrodes.

There has been much debate regarding the utility of MEG in the evaluation of MTLE with HS. When MEG is utilized to determine the electric current dipole in MTLE with HS, the activity is found to be distributed in diverse regions that may be unrelated to the ictal-onset area.⁴⁵ Moreover, there is persistent debate as to whether or not MEG recordings in patients with MTLE can detect mesial temporal interictal epileptiform discharges (spikes). Wennberg and colleagues found that intracranially detected spikes localized to the mesial temporal structures could not be detected with extracranial MEG, which suggests that this noninvasive source localization technique may be unable to identify true mesial temporal spikes.⁴⁶ In their data, classic anterior or midtemporal spikes recorded with MEG seemed to be generated in anterior and lateral temporal neocortical structures and were neither propagated from nor to the mesial temporal region.⁴⁶ Another study found that current dipole orientation and distribution of epileptiform activity correlates with cortical thinning in left MTLE with HS.⁴⁷ These results suggest that regardless of the presence of HS, in a subgroup of patients with MTLE a large cortical network is affected.⁴⁷ MEG is more commonly used when neocortical epilepsy is suspected because relevant lesions are often small and easily missed during routine MRI review, or too large to be completely resected and the area of interest needs to be defined.

Functional MRI (fMRI) evaluates cerebral blood flow by looking at the difference between venous oxyhemoglobin and deoxyhemoglobin. This is called the blood-oxygenation-level-dependent (BOLD) contrast technique. When certain functional areas in the brain are activated, there is an increase in local metabolism and oxygen consumption. This MR technique may be helpful in the lateralization and localization of language functions when planning for an extended temporal lobectomy. Generally, good concordance exists between fMRI and the WADA test.⁴⁸ However, there are certain requirements that need to be met to enable its utility, including a battery of paradigms that can be administered to patients in a clinically feasible time. fMRI is also believed to be a valid tool for assessing verbal memory lateralization in patients with mesial temporal lobe epilepsy.^{49,50} However, activation statistical maps produced with fMRI sometimes reveal noisy data that may be difficult to interpret, and the specific paradigms for verbal memory may be difficult to develop. Despite its limitations in the lateralization of verbal memory, fMRI studies have shown that functional adequacy of the left hippocampus is the best predictor of postoperative memory outcome.^{51,52} In most centers, this technique is commonly used for the lateralization and localization of language functions, and in some specific cases for the lateralization of verbal memory.⁵³ However, overall, most centers still rely on the WADA test for the definite lateralization of verbal memory.

Malformations of Cortical Development

Malformations of cortical development (MCD) result from disruptions in the complex process of human brain cortex formation and are highly associated with severe epilepsy (—Fig. 2). Modern advanced imaging techniques have im-

proved not only our ability to detect and characterize MCD, but also to identify associated functional abnormalities that are far beyond the visualized structural lesions. The gain in spatial resolution with increasing magnetic field strength (now up to 7T) and subsequent increase in signal-to-noise ratio, can potentially increase the degree of anatomic detail obtained in complex brain malformations.⁵⁴ Advances in multichannel coil technology with phased-array surface coil have increased resolution and contrast of the acquired images, with maximum gains in the cortical surface.⁵⁴ Recent MR advanced sequences improve image quality and might be helpful in the characterization of MCD. For example, the volumetric T1WI with spatial resolution (SPGR or MPRAGE) allow high-quality multiplanar reconstructions that favor a more accurate diagnosis.⁵⁵ Also, volumetric FLAIR can be very sensitive for characterizing white matter involvement.⁵⁵ Despite these advances, clinical information is still necessary for guiding the intensive and time-consuming visual search required in the evaluation of volume acquisitions with multiplanar reformats, which are in the order of millimeters. Computer-assisted methods, such as voxel-based morphometry (VBM), may be helpful in the detection of subtle lesions.⁵⁶ However, automatic approaches are supplementary to human visual inspection, and typically inaccurate when used in isolation.^{54,56}

Although conventional MRI with high spatial resolution identifies the malformed cortex in a large number of cases, recent investigations have focused on associated abnormalities in the white matter identified by DTI and tractography.⁵⁷ Some studies have shown a reduction in the white matter in the affected hemisphere containing the MCD and more widespread alterations in diffusivity and anisotropy that could be of potential clinical importance if surgery is considered.⁵⁸

Although hypometabolism in interictal ¹⁸F-FDG PET studies can help in delineating the epileptogenic region, it appears that this technique does not contribute toward elucidating the underlying etiology when the MCD is not obvious or well defined on MRI. For example, it is not helpful in differentiating focal cortical dysplasias (FCD) from mixed neuronal and glial tumors.⁵⁹ The presence of regional interictal hypometabolism, however, may guide the intensive search for a subtle MCD in patients with cryptogenic epilepsy. Unfortunately, the sensitivity of PET in extratemporal epilepsy is lower than in TLE, ranging between 30% and 50%.³² Nevertheless, when a metabolic abnormality is detected, ¹⁸F-FDG PET/MRI coregistration appears to enhance the noninvasive identification and successful surgical treatment of patients with MCD, especially mild focal cortical dysplasia (FCD).⁶⁰ SPECT perfusion difference has also been used with the same purpose.

Current data demonstrates the utility of MEG for providing (1) functional concordance for the majority of structural lesions, and (2) useful data for identification of previously unappreciated lesions.⁶¹ These advantages are especially important in the presence of multiple MCD and, in presumed nonlesional cases where a mild MCD (for example, FCD) is suspected. MEG may detect interictal epileptiform activity in up to one-third of EEG-negative patients, especially in the

Fig. 2 Malformations of cortical development. (A,B) Coronal and axial T2-fluid attenuated inversion recovery magnetic resonance imaging (FLAIR MRI) of a 34-year-old right-handed man with frequent convulsive seizures shows left superior temporal gyrus focal cortical dysplasia. There was no mass effect or abnormal enhancement associated with the lesion. (C) Axial T1-magnetization-prepared rapid acquisition gradient echo magnetic resonance imaging (MPRAGE MRI) of a 28-year-old ambidextrous man with episodes of left arm numbness and weakness shows right parietal focal cortical dysplasia (arrow). Note the abnormal cortical thickness. (D,E) Coronal and axial T2-FLAIR MRI of a 28-year-old left-handed man with nonconvulsive seizures, which are each preceded by tingling and tightness in the right face, shows left temporoparietal subependymal and subcortical gray matter heterotopia. (F) Proton density MRI of a 37-year-old right-handed man with complex partial and convulsive seizures shows bilateral polymicrogyria (arrows).

case of lateral cortical epilepsy and/or FCD.⁶² In the evaluation of the epileptogenicity of MCD, MEG is considered a valuable complementary tool to EEG.

Another important aspect of the evaluation of MCD in epilepsy is the possibility that regions of malformed cortex might retain a functional role. This likely depends to a significant extent on the severity and distribution of the malformation or on the usual functional role subserved by the affected region of cortex.⁶³ When epilepsy surgery is being considered, this question is usually addressed with the aid of functional imaging modalities, such as fMRI and MEG.

Some of the MCD with highest epileptogenic potential and radiologic significance are hemimegalencephaly, lissencephaly, schizencephaly, polymicrogyria, heterotopias, and FCD. Each type of MCD is characterized by particular radiologic features that allow its identification and differentiation. An accurate diagnosis is especially important for surgical planning and determination of prognosis.

Hemimegalencephaly is a rare malformation that affects an entire hemisphere. Imaging characteristics are abnormal gyration, thickened cortex, loss of gray white matter differentiation, and signal changes on T2-weighted images.⁶⁴ The

contralateral hemisphere usually appears normal on imaging. However, this does not exclude the possibility of abnormal pathology, which may be epileptogenic as well.⁶⁵

Polymicrogyria, schizencephaly, and lissencephaly are further forms of MCD characterized by abnormal gyration patterns. In polymicrogyria, there are too many small gyri separated by shallow sulci. In schizencephaly, an abnormal cleft is lined by polymicrogyric cortex. Lissencephaly is characterized by the absence of gyri. In addition to the abnormal gyration patterns, MRI may demonstrate blurring of the gray-white junction and cortical signal abnormalities.⁶⁶ Some reports suggest that in this type of MCD, the visualized abnormalities are probably not the most important component of the epileptogenic zone, which may be spatially distributed.⁶⁷

Subcortical and periventricular nodular heterotopias are characterized by the abnormal presence of gray matter in the white matter. These are typically more subtle than the abnormalities in gyration patterns, and histopathologically characterized by an overlying dysplastic cortex.⁶⁷ Evaluation by stereo-EEG has shown that ictal activity starts from the overlying cortex, or simultaneously in nodules and cortex.⁶⁸ Heterotopias are usually seen as multiple lesions, or in the

Fig. 3 Low-grade tumor. A 44-year-old right-handed woman who had a first convulsive seizure and was found to have a left temporal brain mass. (A) Axial T2- fluid attenuated inversion recovery magnetic resonance imaging (FLAIR MRI) showed a well-circumscribed round T2 hyperintense lesion in the left temporal subcortical white matter, surrounded by a less distinct region of abnormal T2 hyperintensity extending posteriorly and laterally. (B) Axial T1-weighted MRI following intravenous administration of gadolinium contrast showed a focal nodular area of abnormal enhancement at the anteromedial aspect of the round lesion. (C) Axial gradient echo MRI showed multiple foci of susceptibility artifact, consistent with calcification. The radiographic differential for a cystic and nodular mass with internal calcification in a young person with new-onset seizures includes tumors such as ganglioglioma, dysembryoplastic neuroepithelial tumor (DNET), pleomorphic xanthoastrocytoma, and oligodendroglioma, though the presence of enhancement could be consistent with a higher-grade lesion. This lesion has not been biopsied and will be followed closely over time.

company of other types of cortical abnormalities. Despite these findings, case series suggest that surgical treatment may be beneficial when the epileptogenic zone is carefully located before surgery.⁶⁸

Focal cortical dysplasia is the most common MCD in epilepsy surgery patients.⁶⁹ A study by Kim and colleagues showed a significant relationship between the pathologic grade and the detectability of FCD by brain MRI.⁷⁰ FCD are characterized on MRI as focal cortical thickening with hyperintense T2/FLAIR and hypointense T1 signal abnormalities in the underlying white matter, at times with the aspect of a wedge-shaped tail extending radially to the ventricle.^{54,71–73} Other accompanying imaging findings are focal white matter atrophy, a deep sulcus, and broadening of the gyri adjacent to the FCD.⁵⁵ Often, with FCD, the epileptogenic zone is more extensive than the lesion visualized.⁷² In fact, at times, the lesion can be quite subtle, and FCD accounts for a significant proportion of patients with intractable focal epilepsy whose MRIs are considered normal.^{74,75} Palmini et al proposed a classification of FCD into two types with two subtypes each based on the presence of changes in the cortical architecture and the presence of dysplastic neurons, giant neurons, or balloon cells on histopathology.⁷⁶ The discussion of this classification is beyond the scope of this article. However, it is important to mention that current MRI is only moderately sensitive to detect FCD, independently of the type, because 31–41% of patients with FCD type I and 21–33% of patients with FCD type II have no MRI abnormalities.^{77,78}

Low-Grade Intra-Axial Tumors

The most common tumor types in patients with intractable epilepsy are ganglioglioma and low-grade astrocytoma.⁷⁹ Less

common are low-grade oligodendroglioma, mixed glioma, and dysembryoplastic neuroepithelial tumor (DNET).⁷⁹ Although gangliogliomas occur with an overall frequency of less than 1% of all patients with brain tumors, almost all patients with this tumor type have epilepsy. Like ganglioglioma, DNET is almost exclusively found in patients with epilepsy (►Fig. 3).

Gangliogliomas are encountered in up to 38% of the patients with brain tumors undergoing surgery for refractory seizures.⁷⁹ These tumors occur more commonly in children and young adults.⁸⁰ The tumor is usually single, well circumscribed, and located in one of the temporal lobes.⁸⁰ Almost 60% of gangliogliomas have a cystic component; some even consist of a large cyst with a mural nodule. The most common MRI findings associated with the solid component include increased signal on T2WI, isointense signal on T1WI, and significantly increased signal on proton density images. There is contrast enhancement in ~40% of cases.⁸¹ The cystic component usually exhibits increased signal on T2WI, decreased signal on T1WI, and variable (depending on protein concentration) signal on proton density images.

DNET is typically diagnosed before the age of 30. The lesion is supratentorial, often well demarcated, and usually found in temporal or frontal lobes.⁸² The characteristic MRI finding is increased signal on T2WI associated with decreased signal on T1WI. Contrast enhancement has been described in up to one-third of patients.⁸³ Also approximately one-third of the patients exhibit cystic changes, and one-fourth demonstrates calcification.⁸⁴ On proton density images, the signal from cystic-appearing DNET is different from that of cerebrospinal fluid, implying an increased protein concentration, and thereby distinguishing these tumors from subarachnoid cysts.⁸³

Gangliogliomas and DNET cannot be reliably differentiated from each other and from other types of low grade tumors

using current MRI techniques (including MRS) or ^{18}F -FDG PET. However, prognosis in patients with low-grade tumors appears to be related to location rather than histologic appearance.⁸⁵ For the most part, these tumors are benign. If a complete resection of the tumor can be accomplished, the prognosis for seizure control is excellent. One factor that can affect seizure outcome is the coexistence of tumors and FCD. FCD are often seen near but separate from the tumor.⁸⁶ Some authors believe that this finding suggests a dysplastic nature of the tumors.⁸⁶

Meningiomas

Meningiomas constitute the most common extra-axial neoplasm of the brain. Epilepsy is one of the most common symptoms of intracranial meningiomas with an incidence of 20–50% as the initial symptom.⁸⁷ Location of the meningioma at the supratentorium or convexity and evidence of severe peritumoral edema have been associated with the development of epilepsy.⁸⁷ Surgical excision of the meningioma stops the seizures in ~60% of the patients.⁸⁷ Hence, the importance of its accurate identification.

On unenhanced CT, ~60% of meningiomas are slightly hyperdense compared with normal brain tissue.⁸⁸ Also, calcifications within meningiomas can be seen in ~20% of cases.⁸⁸ Their extra-axial nature is suggested by a sharp interface with displaced brain parenchyma, the presence of a cerebrospinal fluid attenuation cleft and intense tumor postcontrast enhancement.⁸⁹ Enhancement is usually homogeneous, but can show some heterogeneity depending on the consistency of the tumor, i.e., the presence of calcium, fat, and tumor necrosis.⁸⁹ Hyperostosis of adjacent skull is highly suggestive of benign meningioma and is best demonstrated by CT, windowed on bone algorithm, as cortical bone thickening and hyperdensity.⁸⁹

MRI is superior to CT in detecting the full extent of meningiomas, vascularity, and intracranial edema.⁸⁸ The typical MRI signal intensity characteristic of meningiomas consist of isointensity to slight hypointensity relative to gray matter on the T1WI and isointensity to hyperintensity relative to gray matter on the T2WI. In addition, there is avid homogeneous enhancement following the administration of gadolinium, and an enhancing “dural tail,” which reflects neoplastic dural infiltration or reactive vascularity, or both, draining into the adjacent dura.⁸⁹ Occasionally, meningiomas may have necrotic centers or calcified portions, which may not enhance. Meningiomas can be nearly spherical or elongated (en plaque), multiple, and often originate from a dural sinus. Although most meningiomas have no metastatic potential, they may result in serious complications secondary to dural sinus invasion, narrowing and thrombosis of important vascular channels, and compression of important neural structures.⁸⁹ The degree of parenchymal edema is variable in meningiomas, and it seems to correlate with the size and location of the lesion as well as its rate of growth. Although there are exceptions, larger meningiomas located adjacent to the cortex tend to incite greater edema than smaller meningiomas or than those along the basal cisterns and planum

sphenoidale. Edema associated with meningiomas may be caused by compressive ischemia, venous stasis, aggressive growth, or parasitization of pial vessels.⁸⁸ Malignant meningiomas occur uncommonly, and these are usually diagnosed when the meningioma exhibits intraparenchymal invasion or markedly rapid growth. Reduced water diffusivity has been correlated with more aggressive tumor behavior and is sometimes seen with atypical/malignant meningiomas.⁹⁰ A decrease in ADC values on follow-up of a benign meningioma should raise suspicion for dedifferentiation to a higher tumor grade.⁹¹ However, the utility of this finding is limited by the inability of DWI to identify histologic subtypes. On MRS, meningiomas are characterized by prominent Cho, absence of NAA and Cr, and presence of Ala.⁹² This spectral pattern has been reported in both typical and atypical meningiomas and, MRS cannot reliably differentiate one type from the other.⁹²

The role of PET imaging in the evaluation of meningiomas is complicated by the variable metabolic presentation in different meningioma types. Given the presence of hypermetabolism in malignant meningiomas, some authors have proposed the use of ^{18}F -FDG PET for the differentiation of benign and malignant meningiomas as well as for the noninvasive prediction of tumor growth.⁹³ However, the presence of hypermetabolism confounds their differentiation from other intracranial tumors.

Conventional angiography is most often performed for preoperative endovascular embolization and is intended to minimize blood loss intraoperatively. Meningiomas diagnostically appear as lesions with an angiographic stain (tumor blush) and can have both dural and pial blood supply.

Neurocutaneous Disorders

The neurocutaneous syndromes are a group of unrelated disorders characterized by congenital dysplastic abnormalities involving the skin and nervous system. Seizures are encountered most frequently in tuberous sclerosis complex (TSC) and Sturge-Weber syndrome.

TSC is a multisystem, autosomal dominant, genetic disorder with wide phenotypic variability. Brain involvement occurs in 95% of individuals with this condition. Approximately 80–90% of patients develop epilepsy attributable to the neuroanatomic abnormalities associated with TSC, including cortical tubers, subependymal nodules (SN), and subependymal giant cell astrocytomas (SGCA) (►Fig. 4).⁹⁴ However, the exact pathophysiology of epilepsy in TSC is not well understood.

The SN are usually multiple and lie in the lateral ventricles, typically near the body of the caudate or foramen of Monro. They are often less than 1 cm in diameter and do not enhance with contrast. Calcification of SN is common after 18 months of age. On T1WI, SN are isointense to white matter and slightly hyperintense compared with gray matter. They are isointense or hypointense on T2WI, which may show a central area of decreased signal. Overall, SN are better seen on T1WI, whereas cortical tubers are better seen with T2WI.⁹⁵ Cortical tubers appear on MRI as multifocal areas of increased T2 signal

Fig. 4 Tuberous sclerosis complex in an 8-year-old boy with mental retardation, autism, and epilepsy. Seizure types include infantile spasms, drop attacks with loss of consciousness, and tonic spells. (A,B) Axial T2-fluid attenuated inversion recovery magnetic resonance imaging (FLAIR MRI) shows innumerable hyperintense cortical tubers. (C) Axial T1-magnetization-prepared rapid acquisition gradient echo (MPRAGE) MRI shows subependymal nodules (arrows).

affecting the cerebral cortex, deep white matter, or most often, both white matter and cortex. SGCA may occur in up to 8% of patients, typically near the foramen of Monro. They are believed to originate from SN, but are differentiated from these by their larger size and contrast enhancement. Patients may also have heterotopic masses of gray matter, consistent with the concept that TSC is a dysplastic process.

In a large number of patients with TSC, epilepsy proves to be refractory to medical treatment. Presurgical evaluation is typically complex due to the presence of multiple intracranial abnormalities with epileptogenic potential. PET scans may reveal hypometabolic cortical lesions corresponding to cortical tubers, and it may also show hypometabolic areas without abnormalities visualized on MRI.⁹⁶ In the same fashion SPECT and MEG can be used in the search for the epileptogenic lesion.^{97,98}

Sturge-Weber syndrome (encephalotrigeminal angiomas) is characterized by a congenital unilateral cutaneous hemangioma (facial port wine stain), hemiplegia, and epilepsy. Neurologic involvement results from the effects of chronic ischemia of the cortex, which is produced by “vascular steal” due to overlying leptomeningeal venous angioma.^{99,100} This phenomenon results in cortical atrophy and intracortical calcifications (→ Fig. 5), which produce the classic tram-track appearance on CT. MRI detects a greater extent of disease than CT, particularly on contrast-enhanced images.⁹⁹ In this instance, the pia enhances dramatically, giving a true demonstration of the degree of the vascular abnormality. Cortical enhancement caused by ischemic injury may also be present. Abnormally low signal intensity within the white matter on T2WI is probably related to abnormal myelination from ischemia.¹⁰¹ Focal perfusion defects are identified on SPECT

Fig. 5 Sturge-Weber syndrome. A 30-year-old right-handed man with simple partial seizures that began at 7 months of age, involving stiffening and shaking of the left arm without loss of consciousness. (A) Axial T2-fluid attenuated inversion recovery magnetic resonance imaging (FLAIR MRI) shows a large region of right parietal cerebral atrophy. (B) Axial T1-weighted MRI following intravenous administration of gadolinium shows abnormal cortical enhancement, consistent with pial angiomas. (C) Axial computer tomography (CT) without contrast shows marked “tram-track” calcification of the cortical gyri.

studies and, PET scan reveals areas of hypometabolism corresponding to the location of the lesions.⁹⁹ However, due to the extensive nature of the vascular abnormality, the surgical options for refractory epilepsy are limited, and restricted mostly to hemispherectomy, and in some bilateral cases, corpus callosotomy.

Cavernous Angiomas

Cavernous angiomas (CAs) are congenital or acquired clusters of dilated sinusoidal vascular channels lined by a single layer of endothelium, without intermixed normal brain.^{102,103} CAs contain blood products of different ages, calcification, and occasionally gliosis. CAs appear as nonspecific high-density regions on CT, sometimes with faint postcontrast enhancement. Angiographically, no feeding arteries are seen, although occasionally an early filling vein or subtle blush may be visualized.¹⁰⁴

MRI has provided increased sensitivity to visualizing these malformations (►Fig. 6). The heterogenous appearance of the core or internal part of a CA results from the presence of blood products at different ages of degradation. On T2WI, both acute and chronic blood products (i.e., oxyhemoglobin, deoxyhemoglobin, and hemosiderin) appear hypointense and subacute blood products (i.e., methemoglobin) appear hyperintense. The heterogenous appearance of the core has been likened to the appearance of a kernel of popped popcorn.

The outer rim of the cavernous malformation is T2 hypointense due to chronic blood products at the interface between the CA and surrounding brain parenchyma.¹⁰⁵ GRE or SWI sequences are highly sensitive for detecting CAs, though the intrinsic “blooming artifact” associated with these sequences can actually obscure the smaller structural features of the malformation. Edema and mass effect are not seen with CAs, except in the setting of acute hemorrhage.

These lesions usually do not produce life-threatening hemorrhages, though hemorrhage into and beyond a CA can occur. The effects of a CA primarily result from the location of the lesion. Overall, 35–70% of patients with CA present with seizures.^{103,106} Approximately 40% of these individuals progress to medically refractory epilepsy.¹⁰⁶ A recent systematic literature review revealed that in the setting of a single cavernoma and consistent electroclinical seizures, up to 75% of patients become seizure free after lesion removal.¹⁰⁶ In the same review, the most important predictors of good postoperative seizure control were found to be achievement of a gross total resection and early intervention.¹⁰⁶ In addition, some groups have reported improved seizure outcomes with a more extensive resection including removal of the hemosiderin ring.^{107–109}

Traumatic Brain Injury

Head trauma is responsible for more than 20% of symptomatic cases of epilepsy and 5% of all epilepsy.¹¹⁰ Seizures may begin anytime after the injury. Early seizures, which occur within a week of the injury, are acute symptomatic attacks often accompanied by neurologic or systemic abnormalities. Although not considered epilepsy, these seizures increase the risk for posttraumatic epilepsy (PTE).¹¹⁰ Seizures that occur after a week of the head trauma are thought to reflect permanent changes in the brain, tend to recur, and therefore often represent onset of PTE.¹¹⁰ The most important risk factor for the development of either early or late seizures is the severity of the injury. Greater severity, brain contusion, intracranial hematoma, depressed skull fracture, and dural penetration are associated with increased seizure risk.^{110,111} Although sometimes the severity of the injury is greater than appreciated on imaging, the presence of some of these factors may aid in the identification of individuals that are at increased risk of developing PTE and that may require closer monitoring.

Fig. 6 Cavernous angioma. A 58-year-old right-handed man with partial complex seizures with occasional secondary generalization. (A,B) Coronal and axial T2-weighted magnetic resonance imaging (MRI) shows a well circumscribed lesion in the right inferior temporal lobe. The internal contents of the lesion appear heterogenous (areas of T2 hyper- and hypointensity), due to blood products of varying age. The lesion is surrounded by a confluent rim of T2 hypointensity due to hemosiderin. (C) Axial gradient echo MRI shows susceptibility artifact consistent with blood products.

Imaging of head trauma has a primary role both in assessing the extent of the trauma and in determining the appropriate therapy. The most efficient method to triage for acute head trauma remains CT. It is readily available, fast, and usually very accurate at detecting acute hemorrhage (high density on unenhanced scan) and depressed skull fractures. Rarely, there are isodense or low-density hemorrhages in patients with severe anemia or disseminated intravascular coagulopathy, and these may be more difficult to detect. Another limitation of this technique is the relatively limited visualization of the infratemporal, subfrontal, and posterior fossa regions. When head trauma is evaluated with CT, analysis should include review of brain, subdural, and bone windows. The wide window setting aids in separating high-density blood from the high density of bone, and is particularly useful in acute subdural and epidural hematomas, which can be small and difficult to differentiate from the calvarium.¹¹² Bone windowing is essential to identify fractures.

Overall, MRI reveals the extent of brain damage after head trauma with greater sensitivity than CT.¹¹³ However, few studies have assessed MRI findings in patients with PTE. Angeleri et al obtained MRI scans from 104 TBI patients one year after injury, and found that the presence of cortical or subcortical hyperintense lesions visible on T2WI with accompanying hemosiderin on GRE sequences was associated with an increased risk of PTE.¹¹⁴ Susceptibility-weighted imaging (SWI), which is related to the GRE imaging, takes advantage of susceptibility differences between tissues. This results in enhanced contrast sensitive to paramagnetic properties of intravascular deoxyhemoglobin, i.e., sensitive to venous blood, hemorrhage, and iron in the brain. SWI is frequently utilized for the detection of blood products in the patient with PTE and no apparent abnormalities in other MRI sequences. Diaz-Arrastia et al analyzed high-resolution MRIs in patients with intractable PTE and found that 35% of these patients had HS.¹¹⁵ Often diffuse abnormalities, such as global cerebral atrophy, are seen along with HS.¹¹⁶ Less commonly, dual pathology is noted with HS present in addition to neocortical lesions, usually in the temporal or frontal lobes.¹¹⁶

The exact implications of other more subtle abnormalities, such as diffuse axonal injury (DAI), for the subsequent development of seizures are not completely understood. One study suggests that patients may have isolated DAI on MRI scans yet achieve neurologic recovery without the development of seizures.¹¹⁷ Further investigations are required to corroborate this finding. The radiologic characteristics of DAI are discussed elsewhere.

More recently, novel MRI techniques such as DTI have been used in an attempt to increase the sensitivity of MRI, as well as to gain new insights into the pathogenesis of PTE. DTI permits the examination of white matter integrity in vivo by measuring the diffusivity of water in biologic tissues, as well as an index of the directionality of diffusion. This allows the identification and quantification of microstructural changes that extend beyond the obvious lesions seen on the T2 and FLAIR images. Gupta et al compared DTI

findings in patients with chronic traumatic brain injury with and without epilepsy with those of age-matched controls.¹¹⁸ They found that the mean regional fractional anisotropy (FA) was significantly lower whereas the mean regional mean diffusivity (MD) was higher in patients with TBI compared with controls, and that the mean regional FA ratio was significantly lower in TBI patients with epilepsy than in those without epilepsy.¹¹⁸ This suggests that the severity of injury as predicted by the DTI-derived increased volume of microstructure damage may be associated with PTE. However, their sample was small and further studies are needed to make definite conclusions.

Conclusions

Neuroimaging has provided an extraordinary insight into the pathologic substrate of epilepsy, which is essential for diagnosis, treatment, and determination of prognosis in epileptic patients. MRI is the primary imaging modality for the evaluation of patients with seizures. It allows for the reliable identification of the most common underlying pathologies in epilepsy, including HS, MCD, low-grade tumors, abnormalities associated with neurocutaneous disorders, CA, and sequelae of TBI. Concordance of findings from structural MRI and functional techniques, such as PET, SPECT, MEG, fMRI, and of course EEG, is of great importance in the presurgical evaluation of patients with medically refractory epilepsy.

Acknowledgment

The images in Figs. 1–6 are used with permission from Modern Neurology, LLC.

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