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Neuroimaging in Epileptic Disorders

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1. Introduction

Epilepsy is one of the most common neurologic disorders, and affects about 50 million people around the world. It is a heterogeneous condition characterized by recurrent spontaneous epileptic seizures. There are no age, sex or race discriminations, although incidence of the first epileptic seizure has a bimodal distribution, with peaks in childhood and after 60 years of age (Engel & Pedley, 2008).

According to their localization, epilepsies and epileptic seizures should be classified as focal (or partial) and generalized. Partial seizures begin in a restricted portion of cerebral cortex. Partial seizures are associated with a restricted area of the of the cerebral cortex and are clasified as either simple or complex, depending on the level of conscious awareness. Simple partial seizures are characterized by brief specific neurologic dysfunction, contingent upon the localization of the epileptogenic focus. By definition, they do not compromise consciousness during the event, and might manifest as motor signs (with a focus involving the primary motor area), sensitive symptoms (focus in the primary somatosensory area), autonomic or psychic signs (mesiobasal areas). Complex partial seizures affect the patient's consciousness from the onset of the event. Both simple and complex partial seizures can propagate to the whole brain and become secondarily generalized seizures. Examples of primary generalized seizures are absence seizures, tonic-clonic generalized seizures, and myoclonic seizures. All those three seizure types are generated by epileptic discharges involving both cerebral hemispheres from their onset. By extension, focal epilepsies are characterized by recurrent spontaneous partial seizures, and generalized epilepsies have generalized seizures as their main seizure type.

Epilepsies can be idiopathic (without an identifiable structural cause), symptomatic (due to a structural lesion), or cryptogenic (with a presumed lesion, not detectable by current available neuroimaging methods). Broadly, idiopathic epilepsies (partial or generalized) begin in the childhood years, have a good prognosis, and go into remission during adolescence. The symptomatic generalized epilepsies encompass a group of epileptic syndromes with very poor prognosis, characterized by extremely refractory seizures and accompanied by neurodevelopmental delay. The symptomatic partial epilepsies depict a large spectrum of epileptic disorders caused by several types of brain lesions. A significant percentage of patients who have seizures not responsive to antiepileptic drugs is affected by this type of epilepsy. Surgical treatment becomes a good therapeutic option for these patients, and the identification of the structural cortical lesion causing their epilepsies is primordial for a good postsurgical prognosis (Panaiyotopoulos, 2010).

Although the basic phenomena of the epilepsies are basically neurophysiologic in their nature, neuroimaging techniques have provided valuable contributions for a greater understanding on this matter. Magnetic resonance imaging (MRI) has revolutionized assessment and management of patients with refractory epilepsies. Several pathological processes affecting the central nervous system can be identified using MRI and related techniques. Brain lesions classically associated with epilepsy, like hippocampal sclerosis, cortical malformations, gliosis, vascular disorders, and small brain tumors often were not visualized using old techniques, named cranial skull X-ray and brain computed tomography (CT). When it is possible to detect a structural lesion underlying an epileptic condition, the prognosis can be better defined, and the most appropriate treatment (e.g., drug vs. surgery) can be indicated with greater confidence (Mc Donald et al., 2000).

Standard MRI has a fundamental role in epilepsy surgery: to identify the epileptogenic lesion, depicting its topographic relationships with eloquent regions of the brain. Magnetic resonance spectroscopy (MRS) measures metabolites in a defined region of interest, and provides important lateralization information for temporal lobe epilepsies, and localization of neocortical epilepsies. Functional MRI (fMRI) focuses on the identification of eloquent cortex to be spared in planning epilepsy surgery, with the intention to improve outcomes by minimizing postoperative deficits. Diffusion MRI allows visualization of brain tracts, improving the study of epileptic circuitries. Magnetoencephalography (MEG) is a technology used to record spontaneous and evoked magnetic fields generated by cortical neuronal activity, and provides additional data to spike detection primarily performed by electroencephalogram (EEG). Because epilepsy is a functional disorder, several invaluable data can be obtained studying epileptic patients with positron emission tomography (PET) and single photon emission computed tomography (SPECT). PET can map numerous physiochemical brain processes, and ictal SPECT allows measurement of brain perfusion patterns during seizures, which is useful in the preoperative assessment of epileptic patients. Current software development enables integration between a variety of imaging data, aiming to minimize the use of invasive techniques in the investigation of surgical candidates, reducing risk and maximizing results (Duncan, 2009).

In this chapter, the role of different neuroimaging techniques in the study and management of epilepsy will be described and evaluated. A brief description of the technique will be followed by indications and main findings contributing for the comprehension of the epileptic disorders. Because detection of a brain lesion is the first step for a successful surgical treatment of epilepsy, emphasis in the presurgical assessment of epilepsy surgery will be given.

2. Structural magnetic resonance imaging

Brain MRI is an important tool to define the presence of a structural abnormality responsible for epilepsy. Acquiring appropriate epilepsy-focused MRI of high quality and diagnosing the important lesions with high sensitivity and specificity are imperative to the definition and understanding of structural brain abnormalities in patients with epilepsy. Moreover, surgical treatment of epileptic patients has a better general outcome when a structural lesion is identified by MRI and further resected. However, brain MRI may be normal in up to one third of patients undergoing anterior temporal lobectomy for refractory temporal lobe epilepsy (Radhakrishnan et al, 1998).

The technique of MRI is based on the intrinsic properties of atomic nuclei of charge, spin, and magnetism. These properties are enhanced in certain nuclei such as hydrogen, phosphorus, and sodium, which are natural components of the brain tissue. They behave as bar magnets and, when submitted to a magnetic field, will align along the direction of the field. In addition, the nucleus possesses another intrinsic property, which gives it a continuous rotary motion around the nuclear axis. This property is called nuclear spin, or spin angular momentum. Because of the combination of nuclear magnetism and spin, the nucleus rotates around both the direction of an external magnetic field and its own axis. The frequency of the precession around the magnetic field is characteristic of the particular nucleus and the direct linear relationship between frequency and the strength of the magnetic field is fundamental to NMR. This is the ground of the improvement of signal-to-noise ratio (SNR) in MR images acquired in a 3 T scanner is improved with respect to images acquired in a standard 1.5 T scanner, as there is a doubling of the fundamental precession frequency.

There are two discrete possibilities for the direction of the precession: one for the nucleus aligned along the direction of the external magnetic field and another one in the opposite direction (anti-aligned). The former state of alignment is preferred and the majority of nuclei will assume this state (low energy). However, a certain proportion of the nuclei will be anti-aligned (high energy) and it is this population difference that underlies the phenomenon of NMR. In the presence of a pulse of electromagnetic waves whose energy corresponds to the difference between these two states, the energy from these waves will be absorbed by the system and the populations of spins in the two states will be equalized. This perturbed state is temporary and, once the application of the electromagnetic waves is terminated, the nuclei will return to the initial state. The energy previously absorbed by the system will hence be returned in the form of a signal that can be detected by a suitably placed receiver coil. By imposing conditions on the system using magnetic field gradients, this signal will reflect not only the nuclear species from which it originated but also its spatial location. A spatially encoded map of these signals can thereby be formed. As water (H₂O) forms more than 80% of the human body, the nucleus of the hydrogen atom is especially suitable for this technique.

Dedicated protocols for imaging in epilepsy patients have been developed to focus the suspected regions of interest (Jackson and Badawy, 2001). A typical clinical scanning protocol for a patient with refractory epilepsy may include T1-weighted imaging, T2-weighted imaging, fluid-attenuated inversion-recovery (FLAIR) imaging, and threedimensional volume acquisition sequences. This protocol is the basis of the initial screening study used to obtain structural information with good morphology and signal data (Table 1).

T1-weighted imaging (short repetition time [TR] and echo time [TE]) is commonly used to initially define the brain anatomy; thus cerebrospinal fluid (CSF) is black, gray matter is gray, and white matter is bright. These images take longer and have thicker slices and often incomplete brain coverage, but they can be extremely helpful in difficult cases. T2-weighted images (long TR, long TE) usually show the CSF as white and the gray matter of higher signal (brighter) than the white matter. These images typically show pathology as areas of increased signal and are used to assess whether the tissue is abnormal. On FLAIR images, the CSF appears dark, which helps to identify lesions with long T2 relaxation times. Pathology still looks high in signal (bright). In the case of epilepsy, the issue of most concern relates to subtle signal changes in the mesial temporal regions on coronal images, in which these artifacts need to be interpreted with an experienced eye.

	TR	TE	TI	Flip	Thickness	Matrix
T2 cor FSE	5000	85		90	4 skip 1	512 x 256
FLAIR cor	8000	129	2200	90	4 skip 1	256 x 224
T2 cor IR	5500	20	200	90	4 skip 0	256 x 256
T1 sag	2000	7,5	750	90	5 skip 2	256 x 256
T2 ax FSE	5000	85		90	5 skip 2	512 x 256

Table 1. Protocol used in MRI exams for epileptic patients at the Service of Radiology of Hospital de Clínicas de Porto Alegre.

A variety of pathologic etiologies are able to be detected using a dedicated epilepsy protocol, with characteristic appearances that may be present, including mesial temporal sclerosis, cortical dysplasia, primary tumors of the brain, vascular malformations, and encephalomalacia. Mesial temporal or hippocampal sclerosis is the most important single cause of intractable MTLE found in surgical series, and it is the most common target for people with epiepsy that requires surgical treatment for refractory complex partial seizures in adulthood. A large body of data confirms the validity of structural abnormalities detected on MRI in pathologically proven HS. HS is histologically characterized by gliosis and neuronal loss in the hippocampus. However, extrahippocampal pathology is often found elsewhere in the temporal lobe, including white matter (Wieser et al., 2004). The key abnormalities in HS are hippocampal atrophy and hyperintense signal on T2-weighted images (Figure 1).

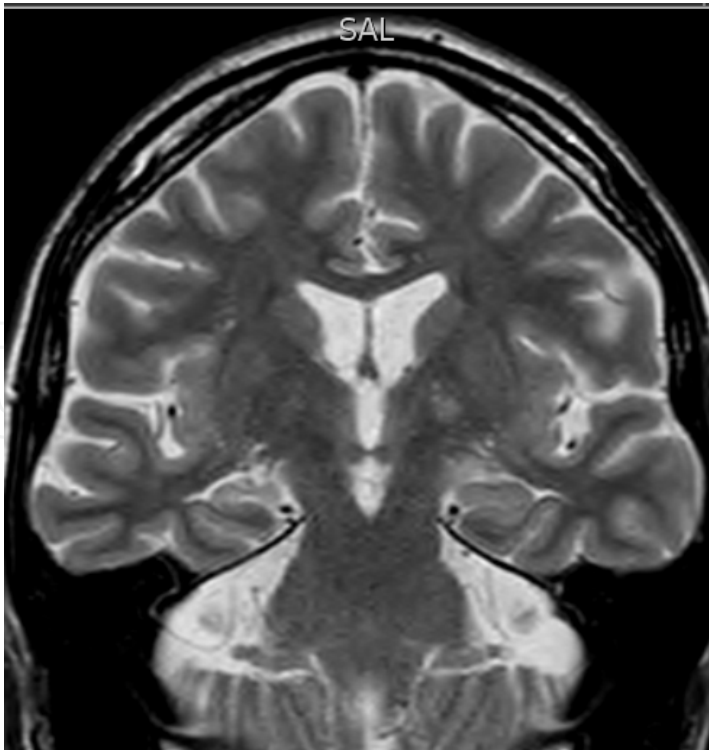


Fig. 1. T2-weighted MRI of right hippocampal sclerosis. Note atrophy and hyperintensity of right hippocampus.

Other MR findings associated with HS include loss of ipsilateral hippocampal head digitations, widening of the temporal horn (Figure 2), and loss of the white matter adjacent to the collateral sulcus (Table 2). In surgical series of TLE, 43-72% of patients with the histopathologic features of MTS can be shown (Wieser et al., 2004).

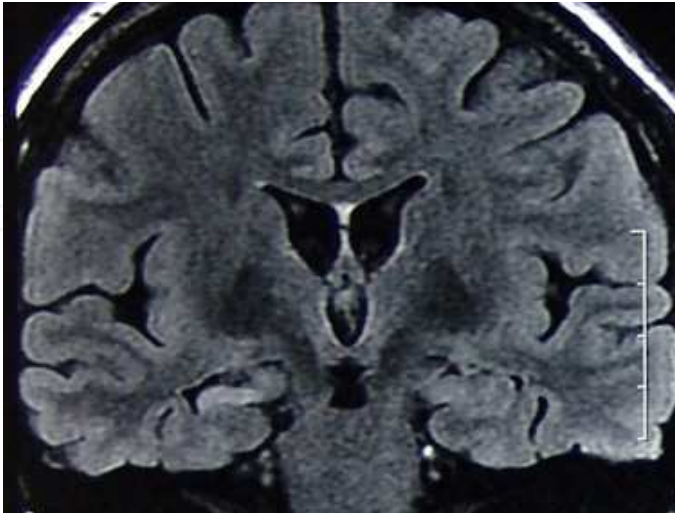


Fig. 2. Right hippocampal sclerosis. Ipsilateral temporal horn dilation and loss of head digitations.

Hippocampal findings	Atrophy Loss of internal architecture Signal changes
Temporal lobe (extrahippocampal) findings	Dilation of temporal horn Temporal lobe atrophy Anterior temporal white matter signal changes
Extratemporal lobe findings	Fornix atrophy Thalamic atrophy Caudate atrophy

Table 2. MRI findings in hippocampal sclerosis.

Dual pathology is present in at least half of all cases of HS. It is nearly always ipsilateral. This can take one of two forms. In the first case, there is a lesion, clearly unrelated to the HS (Figure 3), and it is usually on the same side as the HS. In the second, the MRI shows changes in other parts of the brain that might be related to a common injury that caused both the HS and changes such as unilateral atrophy and anterior temporal lobe changes. Malformations of cortical development (MCD) comprise a number of pathological entities that result from derangements of normal cortical development as a result of either abnormal neuronal proliferation, migration, or organization (Barkovich et al., 2005). Developmental disorders of cortex constitute 4% to 25% of all epileptogenic lesions in adults and 10% to 50% in pediatric epilepsy series (Guerrini, 2005). Focal cortical dysplasias and diffuse cortical dysplasias are heterogeneous groups of developmental disorders defined by an abnormal cerebral cortical cytoarchitecture. Focal cortical dysplasia (FCD) is the most common form of focal developmental disorder, diagnosed in 20-30% of patients with medically intractable localization-related epilepsy.

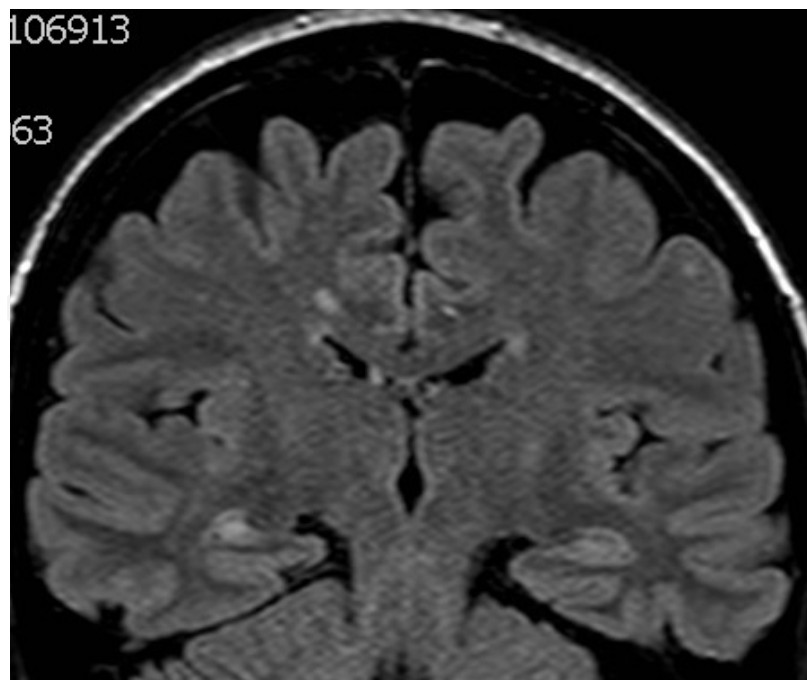


Fig. 3. Right hippocampal sclerosis. In addition, there are several bilateral periventricular hyperintense small lesions.



Fig. 4. Axial FLAIR: left frontal hyperintense subcortical lesion, diagnosed as a focal dysplasia by pathological exam.

MRI has greater resolution than CT imaging and demonstrates abnormal gyral thickening (Figure 4) with underlying T2-weighted white matter changes (Colombo et al., 2003).

Hemimegalencephaly is a disorder of neuronal migration that results in a unilaterally enlarged dysplastic hemisphere. Focal seizures occur in the majority and are typically intractable to AEDs. Hemimegalencephaly may occur as an isolated finding or be associated with other conditions including neurofibromatosis, hypomelanosis of Ito, and the linear nevus syndrome. Brain MRI or CT reveals an enlarged hemisphere with cortical dysplasia with thickening of the mantle or gyri, calcification, other neuronal migrational abnormalities such as schizencephalic clefts (see later), and other anomalies such as agenesis of the corpus callosum. While widespread pathologic changes are seen in the affected hemisphere, microscopic abnormalities have also been noted in the seemingly unaffected hemisphere (Jahan et al., 1997).

Tuberous sclerosis complex (TSC), also known as Bourneville's disease, is one of the common, multisystem, autosomal dominant, neurocutaneous syndromes. TSC presents frequently with infantile spasm or seizures when the congenital hamartomas affect the CNS in addition to other organ systems. Imaging techniques such as CT head scan and MRI scans are diagnostic in many cases, with calcified tubers being readily identified by CT brain scans. Tuber calcification and cortical atrophy are common findings, though cortical atrophy and ventricular dilation are more frequently seen with severe epilepsy and with mental retardation. Tuberous sclerosis has imaging features that are similar to those of Taylor-type dysplasia. There may not be a clear topographic correlation between tubers and the active epileptogenic zone.

Lissencephaly (including both agyria and pachygyria) is the most severe of the known malformations from abnormal neuronal migration. Less severe defects in the same genes and developmental processes result in subcortical band heterotopia. In this group of malformations, neurons begin migration but are unable to complete it. The imaging findings of lissencephaly vary with the severity of the mutation (Guerrini and Parrini, 2010). When very severe, the cortex is markedly thickened and almost no sulci are formed; when less severe, the cortex is less thickened and a variable number of shallow sulci separate broad gyri. In some cases, a 'cell-sparse zone' is identified between the thin outer cortical layer and the thicker inner cortical layer of neurons whose migration has been arrested.

There are three main groups of heterotopia: periventricular (usually nodular: PNH), subcortical (either nodular or laminar) and leptomeningeal, of which only the first two can be detected by imaging. Nodular heterotopia is one of the more common (15-20%) forms of cortical malformation, responsible for 2% of patients with epilepsy. Subcortical band heterotopia or 'double cortex' is a mild form of lissencephaly and classified in that group.

The term "polymicrogyria" defines an excessive number of abnormally small gyri that produce an irregular cortical surface with lumpy aspect. Polymicrogyria can be localized to a single gyrus, involve a portion of one hemisphere, be bilateral and asymmetrical, bilateral and symmetrical or diffuse. Mild forms are difficult to recognize on neuroimaging. The imaging appearance of polymicrogyria varies with the patient's age (Takanashi and Barkovich, 2003). In newborns and young infants, the malformed cortex is very thin with multiple, very small undulations. After myelination, polymicrogyria appears as thickened cortex with irregular cortex white matter junction (Guerrini et al., 2008).

Schizencephaly refers to a full-thickness cleft in the cortex extending to the lateral ventricle and lies near the sylvian fissure. Schizencephaly may be unilateral or bilateral and

represents a neuronal migrational disorder that affects the telencephalon. If the cortical walls are touching the condition is referred to as “closed lip” and, if separated by CSF, then “open lip schizencephaly”. It is thought that schizencephaly and polymicrogyria are similar entities. This is based on the fact that the clefts are lined by polymicrogyria and mechanistically schizencephaly is at the end of the spectrum in polymicrogyria. Whether this is the case in all patients is not known at present.

Pathology plays an important role in determining which patients have seizures. Tumor histology influences seizure frequency, with a seizure incidence of 80-90% for oligodendrogliomas, 60-75% for astrocytomas, 55% for meningiomas, 55% for metastases, and 35-40% for malignant gliomas. Astrocytic tumors constitute about 20% of lesions detected in patients with epilepsy and often involve the parahippocampal gyrus and the amygdala. Although anaplastic tumors or glioblastomas are the most frequent astrocytic tumors; they usually present as a primary tumor problem and are rarely seen in patients with intractable epilepsy. In those patients, fibrillary astrocytomas are most common. MRI typically demonstrates homogeneous masses, with calcifications present in up to 20% of cases. The location is variable, with cortical lesions extending into the white matter and poorly demarcated. Pilocystic astrocytomas are more frequent in children. On MRI these lesions are sharply demarcated and often lobular. Contrast enhancement is typically present as a result of prominent vascularity. Edema is rare, and calcifications are not seen.

Xanthoastrocytomas usually occur in the first decade of life and have a good prognosis. Cystic components are common in this tumor, which usually occurs in the temporal or parietal region. Oligodendrogliomas are histologically characterized by the presence of compact groups of large, rounded cells with empty cytoplasm, often also with mixed glial components. These tumors are less frequent than astrocytomas and uncommon in patients referred for intractable epilepsy, but, when present, they are located within the temporal lobe and tend to involve the amygdala and the uncus and parahippocampal gyrus, with sparing of the middle and inferior temporal convolutions. The underlying white matter often shows tumor infiltration. Mixed glial lesions are a common tumor type in epilepsy (about 5% of foreign tissue lesions). Calcifications are often present. Seizures begin typically in childhood. These tumors are seen predominantly in young patients (b14 years). Gangliogliomas tend to spare the lateral temporal neocortex and involve primarily the mesial structures (Figure 5).

Dysembryoplastic neuroepithelial tumors (DNETs) are a common tumor type in patients with intractable epilepsy [22] (Fig. 11). These tumors are usually located in the temporal region or, less commonly, the frontal region. Cysts are uncommon. DNETs involve both gray and white matter. Imaging findings are quite characteristic and, although not pathognomonic of this condition, should strongly suggest the underlying abnormality. Metastatic spread of tumor to the brain is common and constitutes approximately 20% of brain neoplasms. Seizures are the presenting symptom in about 30% of patients with cerebral metastasis. Metastases have fairly stereotyped localization (gray-white matter junction) and often have peripheral edema.

Seizures are the chief clinical presentation of intracranial vascular malformations, occurring in 24% to 69% of arteriovenous malformations (Kraemer and Awad, 1994) and 34% to 51% of cavernous hemangiomas (Lee et al., 1998). These abnormalities are less frequent in the temporal lobes than in other regions and can be divided into arteriovenous malformations, cavernous angiomas, capillary telangiectasia, and venous angiomas. The MRI features of cavernous angiomas are fairly characteristic. The lesions have a central core with mixed signals indicating blood by products of different stages. Within the core, methemoglobin

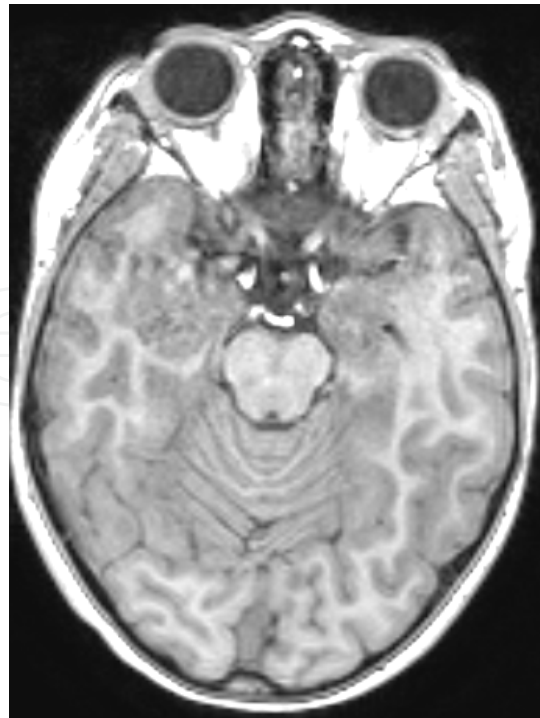


Fig. 5. Heterogenous mass lesion involving the right hippocampus. This ganglioglioma was successfully resected.

It appears as high signals often intermixed with lower signals. Typically, a complete rim of hypointensity surrounds the central core. This rim is usually hypointense on both long and short echoes, with marked hypointensity in the longer echo. These lesions are void of mass effect or surrounding edema, and they should be easily recognized. Venous angiomas are probably the most common vascular malformation, but they are rarely the cause of chronic epilepsy. For tumors and vascular lesions located in or near eloquent cortex, fMRI and DTI techniques provide useful information regarding functionally eloquent cortical regions and important white matter tracts, which may be crucial for resectability.

Cortical gliosis can result from a variety of inflammatory, posttraumatic, and cerebrovascular brain insults. Irrespective of the etiology, gliosis usually appears as a region of increased signal change on T2-weighted images and decreased signal on T1-weighted images, often associated with focal volume loss.

Recent advances in neuroimaging techniques have provided additional benefits to the diagnosis of refractory epileptic patients. Modern 3T MRI scanner and sequences can identify focal abnormalities or clarify uncertain findings previously observed (Strandberg et al., 2008). A voxel-based analysis of FLAIR signal intensity detected malformations of cortical development in individual patients, suggesting that this method may be a useful adjunct to the visual reading of MRI scans (Focke et al., 2008). Recent advances in MRI acquisition, such as the PROPELLER sequence, give improved spatial resolution and definition of hippocampal substructures in vivo (Eriksson et al., 2008). Attempts have been made to automate hippocampal volume estimations. A voxel-based approach using estimations of grey matter content has given promising results. It can provide a quantifiable estimation of atrophy, which can aid in the decision about the presence of clinically relevant HA (Bonilha et al., 2009).

3. MRI spectroscopy

MRI spectroscopy and functional MRI are techniques that may complement anatomic MRI. Magnetic resonance spectroscopy (MRS) is a dynamic test of brain neurochemistry. Minute-to-minute changes in phosphorus permit information that reflects changes in cerebral energy metabolism and pH. So, MRS focuses on providing measures of small low-concentration mobile metabolites. In the presence of magnetic field, molecules and nuclei that have non-zero nuclear spin absorb and emit radiofrequency signals. MRS has identified alterations that occur in patients with TLE with reduction in the neuronal components (represented by the NAA peak) and increase in the glial elements (creatine and choline) to serve as a noninvasive measure of in vivo function. Areas of interest require large areas of brain to sample, and the resolution of MRS is much lower than PET or SPECT. In nonseizional epilepsy, MRS can potentially detect metabolic changes corresponding to the epileptogenic zone. In cases of TLE with normal MRI, NAA ratios can lateralize the seizure focus in 20% of patients (Figure 6).

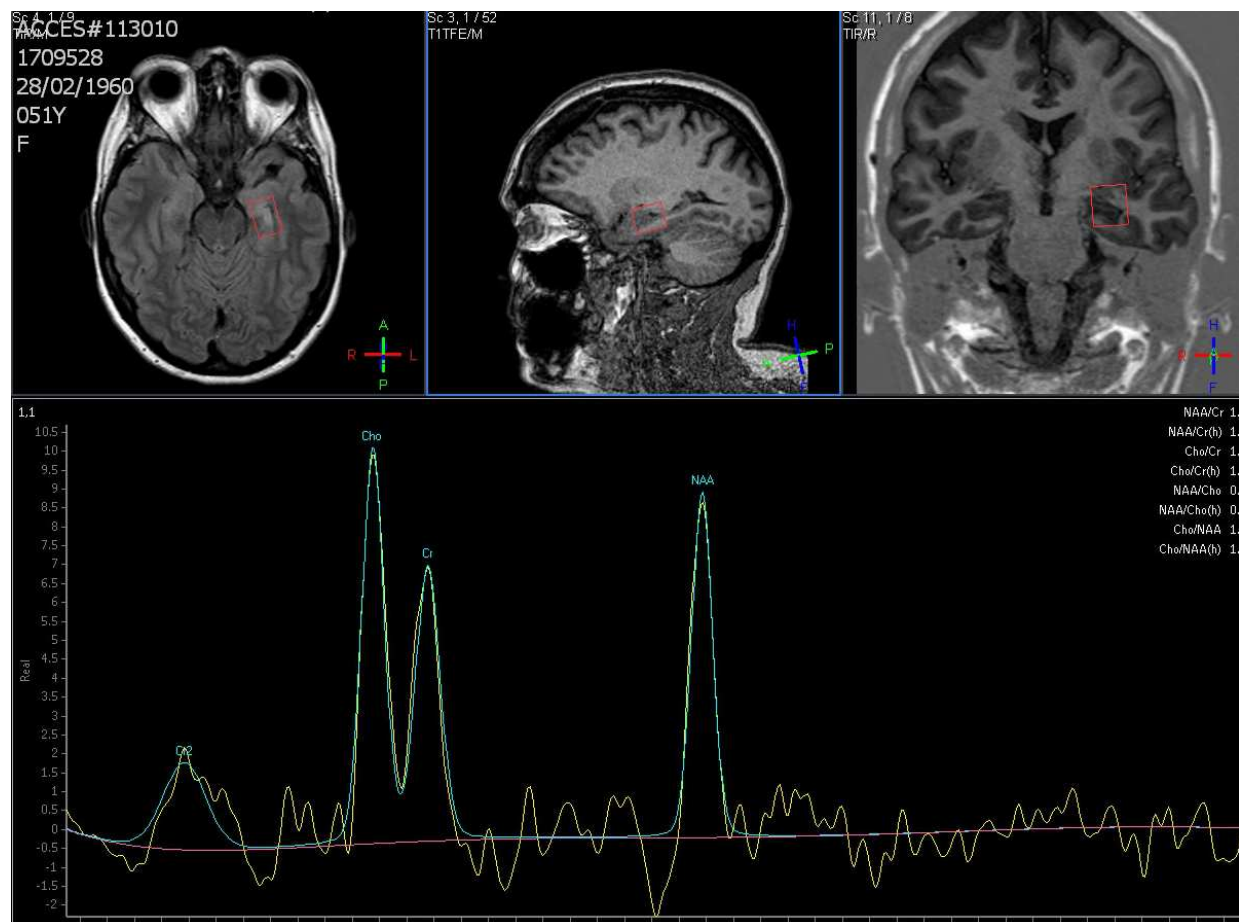


Fig. 6. Left hippocampal sclerosis. Decreased NAA peak.

4. Diffusion MRI

Diffusion tensor imaging (DTI) is an imaging technique performed on a standard MRI scanner that is more sensitive to white matter injury than conventional brain MR imaging. DTI reflects the myelin integrity in vivo and the inherent properties of the cell membranes of

the white matter tracts that restrict the movement of water molecules. Water tends to move preferentially along the horizontal axis of the white matter tracts rather than perpendicular to them (anisotropic diffusion), though the apparent diffusion coefficient (ADC) is the average measure of all directions of water diffusion. The ADC has been considered the surrogate for white matter integrity (Alexander et al., 2007), and DTI may aid in the evaluation of the large fiber white matter tracts. Tractography is user-dependent and very time-consuming. Attempts are being made to automate parts of the process and hence reduce the input needed and the potential bias.

Diffusion-weighted MR techniques are frequently used to assess early signs of cerebral ischemia. Diffusion changes similar to those observed in ischemia may also be present in tumors or infection. Diffusion imaging requires postprocessing, which allows the measurement of summary parameters such as diffusivity and fractional anisotropy.

DTI in malformations of cortical development has demonstrated reduced fractional anisotropy and increased mean diffusivity in the white matter adjacent to cortical dysplasias. The disorganization of the underlying white matter tracts can be detected with DTI fiber tractography. DTI fiber-tracking has been used to map the major motor and sensory tracts in surgical planning of both lesional and nonlesional epilepsy. In temporal lobe resections, preoperative mapping of Meyer's loop can help minimize postoperative visual field defects (Taoka et al., 2008).

Asymmetry of connections between temporal and frontal lobes was a predictor of naming difficulties following anterior temporal lobe resection, with greater lateralization of tracts to the dominant hemisphere being associated with greater decline in naming function (Powell et al., 2008).

5. Functional MRI

Blood oxygenation level-dependent (BOLD) signals are the basis for generating images created using functional MRI (fMRI). In epilepsy, there is neurovascular coupling to define the relationship between epileptiform neuronal activity that is able to be measured by various techniques including SPECT and PET in addition to fMRI. During an increase in neuronal activity there is a simultaneous increase in the cerebral metabolic rate of glucose and oxygen. Greater regional cerebral metabolic rates result in an increase in regional cerebral blood flow and volume to compensate for the increased demand for oxygen. The robust blood supply delivered to the active region of the seizing brain produces an "uncoupling" between the baseline physiologic cerebral metabolic rate of oxygen and the cerebral blood flow by delivering an increased oxygen load. The difference between the rate of oxygen metabolism and cerebral blood flow forms the basis of the BOLD technique used in generating brain fMRI.

Functional magnetic resonance tomography (fMRI) evaluates cerebral functions, and functional deficits and disturbances. fMRI is pursued in particular for three reasons:

1. To identify the seizure focus for resection
2. To identify eloquent function to be spared during epilepsy surgery
3. To investigate the neurobiology of epilepsy

fMRI provides information about how the brain differs in certain epileptic syndromes or it can be used to assess brain abnormalities in an individual patient. fMRI can also highlight the link between abnormal epileptiform activity, network brain activity, and

cognitive function. In the clinical situation, fMRI can help to accurately delineate the epileptogenic zone, surrounding eloquent cortex and vital connections between eloquent cortical areas.

Studies of fMRI with simultaneous EEG recordings are revealing more about the spatial distribution of interictal epileptic discharges, and the relation of these sites to the seizure onset zone, as determined with fortuitous ictal EEG-fMRI or intracranial EEG recording and subsequent resective surgery. Paired analyses of cerebral blood-oxygen-level-dependent (BOLD) signal and perfusion during generalized spike-wave activity have shown that the BOLD signal change is on the basis of alterations in cerebral perfusion, indicating preservation of normal neurovascular coupling (Hamandi et al., 2008).

6. Magnetoencephalography

MEG is a noninvasive direct measure of the brain's normally inherent electrophysiologic capability of neurons to produce magnetic fields. Transmembrane ion movements in active neurons generate magnetic fields that may be recorded by external devices. Since the magnetic fields produced by the brain are extremely weak, sensitive superconducting quantum interference devices (SQUIDS) and magnetically shielded rooms are used to record the MEG from neuronal sources within the brain. Epileptiform discharges that have been identified on EEG can be measured by averaging techniques and localized to provide information regarding the direction of current flow. The functional information is often combined with structural information from brain MRI to provide three-dimensional information used in the selection process of patients for respective epilepsy surgery. MEG has a high temporal (in milliseconds) and spatial resolution (in millimeters), in contrast to scalp-based EEG. The depth of the generator can be more easily determined, and the sources are recorded extracranially and do not carry the risk that invasive electrodes present. MEG is unaffected by the skull in contrast to scalp-based EEG.

MEG measures current flow tangentially at the surface of the brain, while EEG measures radial flow preferentially, though the two techniques are complementary, permitting information regarding activity along the banks of the sulci or the tops of the gyri.

A number of studies have reported that MEG is superior to EEG with respect to spike-detection sensitivity and localization relative to extratemporal epilepsy (Ossenblok et al., 2007). The inverse problem of source localization is less problematic with MEG than EEG due to the lack of distortion of the magnetic properties with MEG as opposed to the electrical properties with EEG. Therefore, IEDs are in general more abundant in MEG than EEG, the spikes are of briefer duration, and in many patients subpopulations of IEDs are found with different topographic maps, indicating better localizing properties with MEG for interictal IEDs than with EEG. In addition, there has been clinical value noted in patients with recurrent seizures after epilepsy surgery through resection of clusters of MEG source spikes adjacent to the margins of prior resection.

Evoked potentials (EPs) are reproducible electrical currents generated by the synchronous discharge of thousands of similarly oriented and grouped neurons as a response to particular stimuli or actions. MEG measures the magnetic correlates of EPs, referred to as evoked fields (EFs). Somato- sensory evoked fields (SEFs) are most routinely used for presurgical functional mapping for epilepsy surgery around the Rolandic region (Benifla et al., 2009).

7. Positron emission tomography

Positron emission tomography scanning (PET) and single photon emission computed tomography (SPECT) are functional neuroimaging techniques that provide complementary information to anatomic imaging techniques to image the anatomic characteristics of the brain. The most common radioisotope employed for PET is 2-deoxy-2-[¹⁸F]fluoro-D-glucose (FDG), or 18F-fluorodeoxyglucose (FDG). FDG is transported into neurons in proportion to glucose consumption of neurons and is trapped rapidly in the cells. PET with FDG, therefore, produces a representation of cerebral energy metabolism. The other energy substrate for brain is oxygen, and ¹⁵O₂ PET images can also reflect energy metabolism in brain. This radioactive tag allows heterogeneous rates of regional cerebral glucose utilization to be estimated. In addition to [¹⁸F]FDG to image the regional cerebral metabolic rate, and [¹⁵O] water to measure regional cerebral blood flow, radiolabeled ligands coupled with dopamine and serotonin permit assessment of neurotransmitter synthesis. Furthermore, benzodiazepine antagonists, NMDA, opiates, tryptophan, and serotonin ligands have been used to evaluate receptors in targeted areas of the brain.

PET scanning has proven useful in the localization of seizure foci and in exploration of the underlying in vivo assessment of physiologic functions of epilepsy in humans (Engel et al., 1990). Interictal regional hypometabolism with PET is seen in 60-90% of patients with TLE. Interictal hypometabolism with PET can be used in the decision process for selecting patients for surgery, invasive EEG planning, as well as predicting a more favorable postoperative outcome when localized hypometabolism is present, while bilateral temporal hypometabolism portends a poorer postoperative surgical outcome. A recent meta-analysis showed that in TLE, ipsilateral focal hypometabolism was a predictor of good surgical outcome (Willmann et al., 2007)

PET studies with ¹⁵O water are less reliable for identification of the epileptogenic zone and have not been consistent in predicting postoperative seizure outcome. Still, decreased perfusion (similar to SPECT) is able to identify 50% of patients with epilepsy that reveal an alteration between metabolism and perfusion. PET studies with neurotransmitter receptor markers give clues to neurochemical mechanisms of epilepsy. Opiate receptors, for example, may increase in the region of the epileptogenic zone, possibly as an inhibitory control mechanism, while benzodiazepine receptors decrease.

PET studies suffer from some limitations. They require specialized equipment and personnel and are expensive to obtain. PET studies average metabolic activity over minutes, so rapid events such as seizures are uncommonly analyzed, and briefer events are not able to be detected. Spatial resolution is in theory about 2-3 mm under ideal conditions (superior to SPECT), but in practical application the resolution may be less. Changes in cerebral blood flow and in the concentration of endogenous compounds that may compete with the radioactive label may greatly affect the results. Finally, PET gives little information on cause and effect.

Depression is a common accompaniment of refractory epilepsy, and understanding the mechanism of this is an important goal. Increased binding of a 5HT-1A receptor antagonist, 18F-MPPF, was found in central serotonergic networks, particularly the raphe and contralateral insula, ipsilateral hippocampus and bilateral frontal cortex, and there was a correlation with symptoms of depression (Lothe et al., 2008) The most likely explanation was felt to be reduced serotonin concentrations. Longitudinal studies before and after cognitive behaviour therapy, and pharmacological treatment would be of great interest.

8. Single photon emission computed tomography

Single photon emission computed tomography (SPECT) is a cerebral functional neuroimaging technique using a systemically injected or inhaled radiolabeled tracer to measure regional cerebral blood flow. SPECT uses radiotracers labeled with single-photon-emitting isotopes to produce images of cerebral function that measure regional cerebral blood flow (rCBF), cerebral blood volume, and blood-brain barrier permeability. A radiotracer that is commonly employed to measure regional cerebral blood flow is hexamethylpropylene amine oxime (HMPAO) coupled with ^{99m}Tc (technetium), though other tracers have been utilized. SPECT is similar to PET in that both are functional neuroimaging techniques that measure similar parameters (Figure 7).

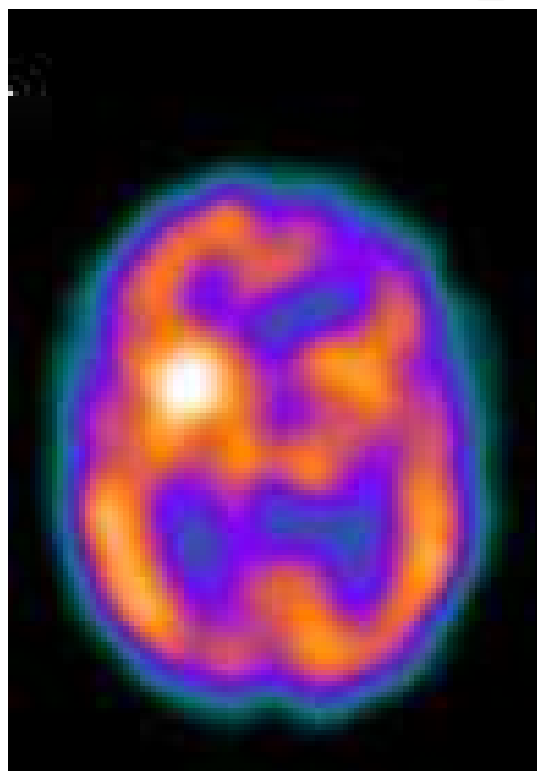


Fig. 7. Ictal SPECT during a right temporal lobe seizure.

Although ictal-interictal subtraction single photon emission computed tomography (SPECT) has been in use for many years as a method of inferring the location of epileptogenic zone, important caveats are still being documented, such as the study of patients with supplementary area seizures in whom ictal SPECT did not localize to the supplementary motor area, but to the anterior cingulate bilaterally (Fukuda et al., 2006).

The accuracy of ictal SPECT analysis is highest when comparing the ictal with interictal perfusion data. Methodologically, this can be done by traditional side-by-side visual evaluation. Visual comparison of interictal and ictal SPECT is less sensitive than subtraction ictal SPECT co-registered with MRI (SISCOM), but ictal SPECT may be localizing in cases when SISCOM was nonlocalizing due to interictal injection during subclinical seizure activity. SISCOM is sensitive, has a good spatial localization, and is the best method to study ictal propagation patterns in the individual patient (Van Paesschen

et al. 2007). For SISCOM analysis, interictal and ictal SPECT scans are co-registered using an automatic registration algorithm based on mutual information and the interictal image is then subtracted from the ictal. The difference image is smoothed and can be transformed into a z-score map using the mean and the standard deviation of the differences in all brain voxels. The mean image of the ictal and interictal co-registered images can be used for co-registration to the patient's MRI.

A meta-analysis of SPECT brain imaging in patients with temporal lobe epilepsy (TLE) showed a sensitivity of ictal SPECT localization of 0.97, relative to diagnostic evaluation without imaging, while this was only 0.44 for inter- ictal SPECT localization (Devous Sr. et al. 1998). Interictal SPECT perfusion imaging on its own, therefore, seems to be inefficient in localizing the seizure onset zone and should only be used as a baseline perfusion measure in the comparison of ictal perfusion images. Ictal SPECT studies of complex focal seizures of extratemporal lobe origin also have an excellent localizing value, but may be more difficult to obtain when the seizures are brief in duration. The sensitivity of ictal SPECT in extratemporal seizures has been reported to be around 90%. Ictal SPECT, and in particular SISCOM images, are predictive of postsurgical outcome independently of MRI or scalp ictal EEG findings (Cascino et al. 2004).

9. Conclusion

To understand the basis of the epileptic disorder, clear definition of the epileptic events (clinical and EEG, functional neuroimaging), the structural abnormalities in the brain, and the clinical context in which seizures occur need to be taken into account. Unless high quality information is obtained in all three of these domains, the basis of the epilepsy in any individual has not been fully assessed. Many levels of information can be acquired using MRI in patients with refractory epilepsy. To make use of all the options available for the investigation of the patient with epilepsy from the perspective of the practicing epileptologist, a well-structured and continuous interaction between the epileptologist and radiologist is necessary. This will lead to acquisition of appropriate epilepsy-focused MR images of high quality and diagnosis of the important lesions with high sensitivity and specificity.

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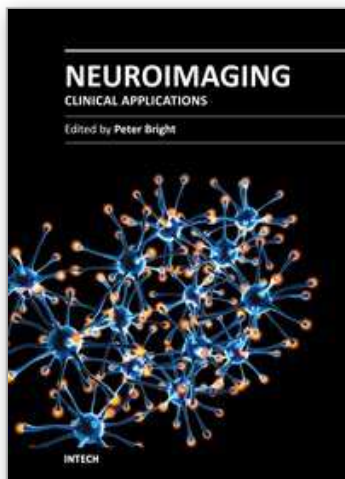
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