Neuroimaging in Epilepsy: A brief review

Michael WL CHEE MBBS, MRCP(UK),

Department of Neurology, Singapore General Hospital

Abstract

Determining the underlying cause of a patient's seizures is a fundamental goal in the workup of epilepsy. Imaging of the brain provides valuable information in this regard. Structural brain imaging reveals morphologic lesions of the brain such as localized atrophy, tumors, vascular malformations and cortical developmental abnormalities. Functional brain imaging shows up biochemical or metabolic abnormalities in the epileptic brain. SPECT (single photon emission computed tomography), MRS (Magnetic resonance spectroscopy) and PET (Positron Emission Tomography) are modalities used. These techniques are technically more sophisticated and less widely available. The principles and benefits underlying their use as well as selected examples are discussed. Finally 'functional MRI' using BOLD (blood oxygen level dependent) contrast as a tool to map out functional brain areas and means to give us insight into epileptic brain dysfunction is introduced.

Key words: MRI, SPECT, PET, epilepsy

AN OVERVIEW

Determining the underlying cause of a patient's seizures is a fundamental goal in the workup of epilepsy. Imaging of the brain provides valuable information in this regard. Structural brain imaging reveals morphologic lesions of the brain such as localized atrophy, tumors, vascular malformations and cortical developmental abnormalities. MRI and CT scanning are the principal modalities. Functional brain imaging produces images reflecting tissue biochemistry, metabolism, perfusion or receptor density. SPECT, MRS and PET are tools used to produce 'functional images'.

MAGNETIC RESONANCE IMAGING

MR imaging highlights differences in NMR relaxation of different brain tissues. This refers to differences in the decay of radiofrequency (RF) signal occurring after the application of RF pulses to the brain, in the presence of a strong magnetic field. Different pulse sequences emphasize tissue differences between T1 and T2 relaxation while suppressing unwanted signals for example, CSF. The goal of using different sequences is to demonstrate these differences in a visually appreciable form. Magnetic resonance imaging is the preferred tool for structural brain imaging. The strengths of MR imaging over CT are its higher resolution, better gray white differentiation and tissue characterization, lack of ionizing radiation exposure and multi-planar acquisition.

Mesial temporal sclerosis

Unilateral hippocampal atrophy is a sensitive and specific indicator of mesial temporal lobe epilepsy. Studies validating the usefulness of MRI include those correlating hippocampal cell loss with extent of atrophy,1,2 surgical outcome with hippocampal asymmetry and neuropsychological performance in relation to extent of hippocampal atrophy.1,3,4 MR abnormalities in mesial temporal sclerosis include signal changes within the hippocampal formation and morphologic changes.4 Increased signal within the hippocampal formation on T2WI, IR6 or FLAIR7 images occurs as a result of T1 and T2 lengthening by pathologic tissue. Atrophy of the hippocampal formation is best appreciated by performing thin slice coronal imaging in a plane perpendicular to the hippocampal formation using one of the many modified gradient echo techniques (eg. MPRAGE, SPGR).8 Atrophy is most frequently seen in the anterior and middle third of the hippocampal formation. Pan hippocampal atrophy is also common. Isolated posterior atrophy is less common. For most clinical purposes, qualitative assessment of properly
acquired images is adequate. A combination of sequences can detect between 80-90% of all patients with MTS. Meaningful comment about minimal to moderate bilateral volume loss is best achieved with volumetric techniques. The latter requires additional hardware and software and is labour intensive." Considerable user experience is needed for consistent results. Another quantitative technique utilizes several measurements of the MR signal during a long TR sequence to plot a T2 relaxation curve. Areas that have prolonged T2 are considered abnormal. This so-called ‘T2 relaxometry’ is requires a special modification of software to perform.

Tumors

Patients with chronic seizure disorders caused by a tumor most commonly have a low grade glial-based neoplasm. These tumors include oligodendroglioma, fibrillary astrocytoma, pilocytic astrocytoma; ganglioglioma and dysembryoblastic neuroepithelial tumors. Imaging features common to all these tumors include localization at or near a cortical surface, sharply defined borders, little or no surrounding edema and, with the exception of the pilocytic astrocytomas little or no contrast enhancement.12

Malformations of cortical development

The introduction of MR imaging has been associated with an increased recognition of malformations of cortical development.13 These are developmental abnormalities resulting from insults occurring between the seventh and 16th weeks of gestation. Previously, some of these malformations could only be diagnosed reliably with a post mortem examination. Focal cortical dysplasia, lissencephaly, “double cortex” or band heterotopia, the bilateral perisylvian syndrome, nodular heterotopia may be visualized.14 Focal cortical dysplasias are the most often considered for surgical resection and perhaps the only lesion in this group other than hemimegaencephaly which is amenable to surgery. There is a range of MR abnormalities associated with this type of abnormality: focal thickening of the cortex, loss of differentiation between cortical and subcortical regions and increased T2 signal within the dysplastic cerebral cortex or no MR change. Thin section three-dimensional volumetric MR imaging may useful in evaluating these anomalies. Reformatted images showing surface anatomy may show up abnormalities not appreciated on 2D sections.15 It is important to realize that some cortical dysplasias are not visualized on MR. These may sometimes be visualized by ictal SPECT or PET.

Focal cortical dysplasia may be a heterogeneous collection of abnormalities. Dysplasias with giant neurons and balloon cells and hemimegaencephaly fall into one group. These individuals tend to have continuous epileptiform discharges and have a higher risk of focal motor status epilepticus. Their seizures are very difficult to control with AEDs. Polymicrogyria/schizencephaly are another group whose prognosis is more benign than with the former group. There is therefore some point in making the distinction between these groups for patient counseling purposes.

Cortical dysplasia is not necessarily associated with severe epilepsy or even epilepsy. A person may have histologically equivalent dysplasia in two cortical sites separated by much space. One region gives rise to seizures but the other does not. Cortical dysplasia tends to spare the hippocampal formation and principally affects the neocortex.

Encephalomalacia or gliosis

Cortical gliosis can occur following any brain injury – trauma, infection. Traumatic insults which produce epilepsy are more frequent with lesions that penetrate the skull and particularly those which penetrate the dura. These areas are recognized by cystic changes within the brain parenchyma with loss of volume of adjacent brain.

Vascular malformations

There are three common types of congenital cerebral vascular malformations: arteriovenous malformations (AVM), cavernous hemangiomas and venous angiomas. Partial epilepsy tends to be associated with cavernous hemangiomas and arteriovenous malformations.12 Seizures may in fact be the only clinical manifestation with these lesions. AVMs are typically be associated with irregular looking flow voids. Cavernous hemangiomas have a fairly distinct appearance on T2 - weighted images: a central region of increased T2 signal intensity surrounded by an area of decreased signal produced by hemosiderin. Cavernomas are most frequent in the frontal and temporal lobes are multiple in about 10% of cases. Familial cavernous hemangiomas tend to be multiple are inherited as an autosomal dominant trait.18

136
FIG. 1: Coronal SPGR MRI showing right hippocampal atrophy at the level of the head of the hippocampal formation

FIG. 2: Axial T2W MR showing a right mesial cavernous angioma.
**SPECT: Single photon emission computed tomography**

SPECT using radioactive $^{99}$Tc tracers, is a technique which detects blood flow changes associated with some types of epileptic foci. Seizures are associated with dramatic increases in cerebral blood flow, localized in partial seizures and global during generalized. Technetium $^{99}$m hexamethylpropyleneamineoxime (Tc-HMPAO, Ceretec(tm)) and Tc-ECD, (ethyl cysteinate dimer, Neurolite(tm)), enter the brain following intravenous introduction and have a very slow redistribution once in the brain. This means that a scan done several hours after the injection will reflect blood flow at the time of injection. Tc-ECD is stable for over 6 hours after being prepared. A dose can be prepared in a nuclear medicine laboratory, brought to an epilepsy monitoring unit, and kept at the bedside for immediate injection during a seizure.

Ictal SPECT provides a higher diagnostic yield than interictal SPECT although both should be compared when making an evaluation. It is vital that injection of $^{99}$Tc be carried out as soon as seizure onset is detected as there is a dynamic evolution of blood flow whereby ictal hyperperfusion switches to post-ictal hypoperfusion. Recent studies suggest that temporal lobe foci may be localized in up to 90% of patients, and false positives are rare. However, if the injection is delayed, hypoperfusion will be found, leading to potential errors. Practically speaking injection should take place within one minute for optimal results. SPECT is a complimentary to structural neuroimaging in the workup of patients with temporal lobe epilepsy. In patients with normal MRI, SPECT can provide fresh information on the locus of the epileptic focus. This may particularly be helpful for the extra-temporal epilepsies in the frontal and parietal regions.

Ictal SPECT has been associated with distinct patterns of cerebral perfusion in subtypes of temporal lobe epilepsy. In patients with hippocampal sclerosis or foreign tissue lesions of the mesial temporal lobe, hyperperfusion was seen in the ipsilateral mesial and lateral temporal regions. In lateral temporal lobe lesions, hyperperfusion was seen bilaterally in the temporal lobes with predominant changes in the region of the lesion. Hyperperfusion was restricted to the ipsilateral anteromesial temporal...
FIG. 4: Axial Tc-HMPAO SPECT images of a 8 year old girl showing an area of ictal hyperperfusion in the right frontal lobe.

FIG. 5: Coronal, Kolmogorov-Smirnov maps of brain activation following a semantic decision task contrasted to a non-semantic task. Auditory (upper panel) and visual words (lower panel) activate similar regions in the left inferior prefrontal area.
region in patients with normal MR and temporal lobe histology but a favorable surgical outcome.36

MR spectroscopy

The evaluation of NMR spectra was the original use of MR before it was adapted to image the brain. Only relatively few molecules which are small, freely mobile can be imaged. Spectroscopy can be performed on different nuclear species. 1H (proton) spectra are most commonly obtained because of the abundance of this species. The biologically significant molecules that can be studied in this spectra at low field are N-Acetyl-Aspartate (NAA), creatine + phosphocreatine (Cr) and choline (Cho) and lactate. Glutamate and GABA can be resolved at 1.5T but as their signals are associated with spin-spin coupling and are best resolved at higher field strength.

NAA is present in neurons, not in glia and its depression reflects neuronal loss. Creatine and Choline are present in oligodendrocytes and astrocytes and their increase in mesial temporal lobe epilepsy are thought to signify gliosis.33 Several studies have confirmed the clinical usefulness of the reduction of NAA/Cr+Cho ratios in the temporal lobe as means of supporting the diagnosis of mesial temporal lobe epilepsy. Abnormalities are not infrequently bilateral but asymmetric. As with other functional imaging tests, the topographical extent of the NAA/ Cr+Ch change exceeds that of the pathologic lesion.32-34 MRS is also useful in supporting the diagnosis of frontal lobe epilepsy although the number of published reports is small. Increased pH and decrease in phospho-monoesters has been reported with phosphorous MRS.35 This requires the use of a different coil tuned to the resonance from 31P from that used for routine structural imaging of the brain and is not commonly available.

With specialized equipment and software, it is possible to estimate brain GABA levels.37 It may one day be possible to determine if a drug with effect on GABA is producing the desired elevation of brain GABA with this technique.

Positron Emission Tomography (PET)

PET uses positron emitting tracers joined to biologically active chemicals (ligands) to study the distribution within the brain of metabolism, blood flow or receptor density depending on the specific ligand.38 18-Fluorodeoxyglucose or FDG is the workhorse ligand used in epilepsy work and is distributed in proportion to regional cerebral metabolism of glucose. The principal clinical application of 18-FDG PET is to support the diagnosis of mesial temporal lobe epilepsy (MTLE). It is sensitive (70-80%) and is associated with a very low false positive rate.39,40 Foreign tissue lesions, neocortical temporal lobe and extratemporal epilepsies are not as well localized.41 In MTLE, the ipsilateral mesial temporal region, lateral temporal cortex and thalamus show glucose hypometabolism.42 Such widespread interictal dysfunction indicates that much more than the mesial temporal structures is involved in the ultimate epileptic disturbance, although the relationship between hypometabolism and degree of epileptogenicity is not well documented.

BOLD Contrast MR for presurgical brain mapping

Neuronal activation results in a regional increase in cerebral blood flow. BOLD contrast MR uses the fact that the magnetic susceptibility of oxyhemoglobin and deoxy-hemoglobin are different and that with neuronal activation there relative proportions of these change regionally. The difference in MR signal during the performance of a task and during a baseline period is used to map brain activated during a specific task. Generation of activation maps is a technically and methodologically complex task.43 To date mapping of visual, somatosensory and motor areas have been used to demonstrate functional areas. The topography of activations obtained from fMRI has been compared with the results of electrical brain stimulation for validation. It is necessary to delineate the extent of clinically critical areas which should be preserved versus brain areas which are activated but whose resection does not adversely affect normal function. The solution of this issue in a robust and reproducible way will be necessary before fMRI can routinely be used as a tool to replace electrical stimulation mapping of functional brain areas.

The mapping of language areas44,46-48 yields results different from what is expected from electrical stimulation and lesion data. The specific brain areas activated are dependent on the choice of active and control task. As such ‘language maps’ obtained differ from those obtained from electrical stimulation.45 However, it is possible to lateralize language function by generating asymmetry indices, comparing right and left hemisphere activations during word generation or semantic decision tasks. This can in selected cases take the place of the language
portion of the intracarotid amobarbital procedure (WADA test).\textsuperscript{40-47}

Activation of the hippocampal formation has been difficult in the past but recent work has shown that this structure can be reliably activated.\textsuperscript{40,30} In an recent study, display of real words or nonsense words in contrast to visual noise led to greater left hippocampal formation activation whereas the contrast between unnamable shapes and visual noise led to right hippocampal activation in normal subjects. Real objects activated both hippocampi.\textsuperscript{50} In the future, tasks may be designed to reveal hippocampal dysfunction seen in persons with mesial temporal lobe epilepsy.

REFERENCES


