IMAGING AND TREATMENT DECISIONS IN SEIZURES AND EPILEPSY

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ABSTRACT

It has been clearly shown that magnetic resonance imaging (MRI) is the preferred modality of structural imaging for both new onset seizures and established epilepsy. MRI imaging in epilepsy requires a dedicated MRI protocol in order to detect subtle epileptogenic lesions such as focal cortical dysplasia or hippocampal sclerosis. Thin-slice thickness and orientation in the longitudinal axis of the hippocampus and perpendicular to it are the main characteristics of dedicated epilepsy MRI. An expert experienced in epilepsy and imaging should interpret epilepsy MRI. The new generation of 3 Tesla (T) MRIs is more sensitive, particularly for focal cortical dysplasia.

Epilepsy-dedicated MRI is indicated particularly at the time of first seizure or new onset epilepsy, and when epilepsy becomes drug refractory. Results of a lesional MRI will assist in classifying the epilepsy syndrome and may well have an influence on treatment planning. Particularly in focal drug refractory epilepsies, a lesional MRI result may indicate a good hypothesis for presurgical assessment. If structural MRI is non-lesional, MRI post-processing may help to identify subtle epileptogenic lesions. CT scanning should only be performed in acute settings if MRI is not available or if the patient is too unwell for MRI scanning.

Keywords: Epilepsy, seizure, MRI, neuroimaging, epilepsy surgery, epilepsy treatment.

INTRODUCTION

Imaging is a standard diagnostic technique in the assessment of seizures and epilepsy. The following review will focus on indication for structural imaging in everyday clinical settings, the most appropriate structural imaging methods, and the impact of structural imaging on treatment decisions with regards to seizure disorders. It reports on imaging for epilepsy syndromes and not for other acute neurological illnesses which may precipitate acute seizures. There is a vast amount of literature on this topic. This review will focus mainly on the key publications.

In principal, there are two main points in time for imaging in seizure disorders: 1) with new onset seizure or seizures; 2) in established epilepsy, particularly at the time when the epilepsy is becoming drug refractory.

IMAGING FOR NEW ONSET SEIZURES

Imaging of new onset seizures is done with two different indications: 1) to identify an acute illness as the underline course for the seizure and possible neurological deficit; and 2) particularly in patients who are not acutely admitted with the first seizure, to establish the aetiology of the new onset seizure disorder.

Acute imaging is done in most settings with computed tomography (CT) of the head, which is usually easily available. CT is able to exclude acute neurological diseases such as stroke, intracranial haemorrhage, cerebral contusion, sinus thrombosis, and skull fractures. Furthermore, the patient is more easily accessible in a CT scan machine than in a magnetic resonance imaging (MRI) machine, which is particularly important if the patient is unwell. However, where MRI is easily available and

safe for the patient, it is also the preferred method for brain imaging in epilepsy.

From the clinical point of view every patient with a new onset seizure, except in some childhood and juvenile epilepsies, is required to have imaging. Patients who have prolonged recovery periods after the first seizure, who present postictally with neurological deficits or signs of infection, should be imaged immediately. Patients who recover quickly, have no neurological deficit, and no signs of infection may be referred for MRI imaging in the first instance, even though this may take a few days or a couple of weeks to be performed.

EPILEPSY SYNDROMES AND IMAGING

Most often clinical diagnoses of epilepsy alone will not lead to the classification of the underlying epilepsy syndrome. Hence, neuroimaging is indicated in most cases of newly presenting epilepsy. It has been shown early on that MRI imaging is superior to CT imaging in epilepsy.[1-3] Most often MRI findings in epilepsy are focal abnormalities such as hippocampal scleroses (HS), malformations of cortical development, and especially focal cortical dysplasia, vascular malformations, tumours, both gliomas and metastasis, as well as post-traumatic scars.[4-6] In generalised epilepsies there may be very complex malformations of brain development such as double cortex, extensive polymicrogyria, or pachygyria. By identifying a structural lesion in the brain, MRI is contributing to the correct classification of the epilepsy syndrome and sometimes even the seizure type.[7]

No imaging is required in clear cases of idiopathic generalised epilepsies such as childhood absence epilepsy (CAE) or juvenile myoclonic epilepsy (JME), if presenting with typical clinical and electroencephalography (EEG) features. However, if these patients are not seizure-free under antiepileptic medication, imaging may well be required to exclude other epilepsy syndromes mimicking idiopathic generalised epilepsy.

MRI in Epilepsy

With the introduction of MRI, many focal structural lesions in the brain, which were not visible in CT scan or other previously used imaging methods, became detectable. A classic example is HS, which MRI findings described early as atrophy and signal increase in the hippocampus.[8,9] In 1997 the International League Against Epilepsy (ILAE) published the recommendations for neuroimaging of patients with epilepsy.[10] Epilepsy patients should be scanned preferably with MRI, using longitudinal relaxation time (T1) and transverse relaxation time (T2) sequences, including, if possible, a 3-dimensional T1 weighted sequence. The sequences should be at least performed in two different orientations, covering the whole brain. Slice thickness should be minimal and an expert experienced in epilepsy should report the imaging. It has been shown that standard MRI imaging of the brain is missing particularly the diagnoses of HS.[11] Furthermore, the comparison of a standard MRI, reported by radiologists and neuroradiologists outside of epilepsy centres, re-reported by neuroradiologists experienced in epilepsy as well as epilepsy-dedicated MRI, reported by neuroradiologists experienced in epilepsy, showed a clear advantage of epilepsy-dedicated MRI.[5]

HS was detected in <10% of standard MRI scans performed and reported outside of epilepsy centres. In contrast, the pick-up rate of HS in epilepsy-dedicated MRI and reporting picked up 100% of histologically proven HS in this group of refractory epilepsy patients undergoing epilepsy surgery. The same study showed similar but not as dramatic differences for benign tumours as well as malformations of cortical development and vascular malformations. Whilst the scan quality improved over the 3-year period of that study, quality of reporting outside of epilepsy centres did not. In the meantime, 3 Tesla (3T) MRI is widely available and has definitely led to a higher pick-up rate in focal cortical dysplasias.[12,13] A head-to-head comparison study between 1.5T and 3T MRI in a large population of patients with epilepsy has not been performed to date.

Epilepsy-Dedicated MRI

As mentioned earlier, MRI imaging is most important to detect lesions in focal epilepsy. A large proportion of focal epilepsy is originating from the temporal lobe. Hence, it is important to focus with the imaging method on the temporal lobe. Axial imaging should be performed within the longitudinal axis of the hippocampus and the coronal slices perpendicular to the longitudinal axis of the hippocampus. In particular, hippocampal and temporomesial structures are much more visible in this way of imaging as in standard MRI brain scans. Standard MRI brain scans are usually orientated in the AC-PC orientation and the hippocampus is cut in an angle of approximately

45 degrees. Therefore atrophy as well as signal increases might be easily missed due to the effect of the angle. Furthermore, coronal images through the hippocampus in the temporal orientation should be acquired with thin-slice thicknesses of 2-3 mm.[14] As practical advice, the coronal temporal orientated sequence should be positioned rather early in the MRI protocol, as patients are more likely to move during sequences towards the end of the examination.

Expected Pick-Up Rate in First Fit MRI

Experiences from first fit clinics show that, depending on the imaging and referral modality, MRI is expected to show epileptogenic lesions in between 14 and 23%.[15-18] The most common epileptogenic lesion is gliosis, most often post-stroke. However, about 10% of the epileptogenic lesions are HS. Malformations of cortical development, vascular malformations, and tumours are around 15% each.[17] Figures may vary slightly as some of the studies performed in large patient cohorts scanned all patients presented to a first fit clinic. Other groups may have a doctor's consultation first and would only image those patients who very likely had a seizure on clinical grounds. Around one-third of patients in first fit clinics may actually have suffered syncope. Furthermore, non-epileptogenic lesions, such as cerebral small vessel disease, unspecific white matter lesions, or global atrophy, are detected in almost the same quantity as epileptogenic lesions. However, the majority of scans are normal at this stage.[16,17]

The likelihood of detecting an epileptogenic lesion in first fit MRI scans increases with age. In a recently published study about imaging in a large first fit clinic, cohort patients over the age of 65 years were more likely to have an epileptogenic lesion than people in younger age groups, although, this difference was not statistically significant. In fact, almost one-third of the elderly patients showed epileptogenic lesions with another one-third showing non-epileptogenic lesions in MRI epilepsy imaging.[17] Interestingly the same study correlated abnormal EEG results with epileptiform discharges and found that focal epileptic discharges are twice as likely to be correlated with an epileptogenic lesion than generalised or normal EEG. Non-epileptogenic lesions in MRI are slightly more likely to show epileptic discharges and generalised discharges compared to patients with normal MRI. 8% of patients with abnormal MRI scans had discordant results in EEG abnormalities.[17]

Expected Pick-Up Rate in Drug Refractory Epilepsy

The majority of studies on MRI lesions in drug refractory epilepsy are from epilepsy surgery programmes. Several studies show that around 80% of patients referred for epilepsy surgery show epileptogenic lesions.[5,6,19] The most frequent pathology is hippocampal or amygdala sclerosis. Furthermore, benign long-term epilepsy associated tumours (LEATs), with mixed cystic and solid components as well as with predominant solid components, malformation tumours, and other low-grade gliomas, are the second largest group with around 17%. Malformations of cortical development, particularly focal cortical dysplasias including balloon cells and tuberous sclerosis, are - with around 15% - the third largest group of epileptogenic lesions in this cohort of patients. Malformations of cortical development such as nodular heterotopia, subcortical band heterotopia, polymicrogyria, and complex brain malformations are included in this group as well. The fourth largest group - with around 13% of all epileptogenic lesions - includes scars of post-traumatic, post-ischaemic, post-haemorrhagic, post-infectious origin, and ulegyria. Rarer aetiologies are oligodendrogliomas, oligoastrocytomas, or high-grade gliomas or meningiomas. Encephalitis including limbic encephalitis and Rasmussen's encephalitis is accounting for <2% of all scans with epileptogenic lesions. Around 6% are down to vascular malformations, with almost 5% alone for cavernomas. However, associated DVAs, arteriovenous malformation, or pial angiomatosis are included in this category as well. Extremely rare cases are hemimegalencephaly, hypothalamic hamartoma, or epidermoid cyst.[19] It has to be emphasised that, particularly in 3T MRI imaging, the detection rate of focal cortical dysplasia has increased.[12,13] Hence the proportion of malformations of cortical development might increase if larger populations are imaged in 3T scans.[20] However, as with the 1.5T scans, it is crucial that epilepsy patients are investigated with the epilepsy-dedicated MRI protocols even in 3T MRI scanners, and that the scans are reported by neuroradiologists experienced in epilepsy or epileptologists.[5,12]

Implication on Structural Lesion and Treatment Decision

Epileptogenic lesions will be crucial in identifying the right epilepsy syndrome. Furthermore, detection of an epileptogenic lesion will have a significant impact on management of the epilepsy, particularly if the epilepsy is becoming drug refractory, i.e. has not responded to two appropriately chosen drugs in adequate dosages to control seizures.[21] In fact, if cavernoma is detected as the underlying epilepsy aetiology, the ILEA recommends exploring epilepsy surgery after the first antiepileptic drug failed.[22] This is down to the fact that cavernomas are responding very well to epilepsy surgery. The likelihood of becoming seizure-free with the second drug is low in this patient group, and cavernomas pose an additional bleeding risk.

Even in the first fit clinic where people may present with generalised seizures in the first instance, detection of a focal lesion may well guide the clinician to use antiepileptic drugs which are primarily used in focal epilepsies.[23] However, if the imaging fails to detect a focal lesion the clinician may well consider using an antiepileptic drug for generalised seizures in that patient. This might exclude the choice of drug, which would suit the patient best with regards to the side-effect profile.[24]

In patients with focal epilepsy becoming drug refractory, a normal MRI brain scan should not withhold referral for evaluation for epilepsy surgery.[5,25] It might be worth at this point of the epilepsy management to confirm the diagnoses of epilepsy in the first instance with video electroencephalogram monitoring as well as performing a further dedicated advanced-epilepsy MRI in order to look for very subtle changes. Even if the structural MRI shows no abnormalities, MRI post-processing may well show abnormalities which could be used as a hypothesis for the epileptogenic focus.[26] Particularly for detection of focal cortical dysplasias, several methods of MRI post-processing have been described in order to identify focal areas of thickened cortex or abnormal grey/white matter differentiation.[27-29]

If an epileptogenic lesion is detected in MRI, the aetiology may also guide towards the success rate of epilepsy surgery.[30] For example, focal cortical dysplasia with balloon cells will have a very high likelihood of seizure control if the cortical part of the lesion can be resected completely.[31-35] HS also shows a high likelihood of a very good outcome in epilepsy surgery, although a recent study has shown that there may be a risk of late relapses in a reasonable number of patients.[36] On the other hand, cortical scars or ulegyria, are less likely to show good surgical outcome.[6] However, there may well be situations where the decision for an epilepsy surgery procedure with this aetiology is still very reasonable.[25]

Recommendations for MRI Protocol

A recent study has focused on the best MRI protocol for epilepsy.[19] The authors analysed, in a very structured approach, the characteristics of different epileptogenic entities on various MRI sequences. They performed a rank analysis of MRI sequences afterwards, which showed that fluid-attenuated inversion-recovery (FLAIR) and T2/short T1 inversion recovery (STIR) sequences are the most important. The authors concluded that the ideal epilepsy MRI protocol should contain six sequences: a 3D-T1 sequence with isotropic voxel size of maximum 1 mm, an axial and coronal T2/STIR sequence, an axial and coronal FLAIR sequence, and a susceptibility sequence for detection of haemosiderin or calcifications in the axial orientation. All sequences should be orientated to the longitudinal access of the hippocampus or perpendicular to it except the 3D-T1 sequence. All axial and coronal sequences should have a slice thickness of 3 mm or less.

One could consider adding a contrast sequence, although the authors state that only pial angiomatosis may be missed, which is an extremely rare entity. Although this study reported a higher detection rate for mesial abnormalities on axial planes orientated along the hippocampal axis, a previous study showed the opposite effect with more mesial abnormalities detected in the conventional axial orientation.[37] Therefore, the orientation of the axial planes remains controversial. However, 3D FLAIR and T sequences, additionally to the 3D-T1 sequence, are used more frequently, and will allow the reconstruction of either axial orientation. An epilepsy-dedicated MRI protocol, like that stated above, should certainly be applied to patients who have drug refractory epilepsy. It might be too time consuming to scan every first fit patient with this MRI protocol, which takes roughly 40 minutes scan time. However, first fit protocols should certainly have all three orientations included as well as temporal orientated coronal FLAIR and T2 weighted sequences.

CONCLUSION

In summary, imaging in epilepsy needs a dedicated approach. Particularly coronal MRI sequences have to be acquired in temporal orientation and thin-slice thicknesses. The reporting radiologist, neuroradiologist, or neurologist should be experienced in epilepsy and reporting epilepsy MRI scans. Lesions can be extremely subtle and may only be detected after several times of studying the scans. At least 20% of all people with epilepsy will have epileptogenic lesions in MRI, the rate being up to four-times as high in people with focal epilepsy. Detecting an epileptogenic lesion in MRI may well guide the clinical classification of the epilepsy syndrome and seizure type and therefore, help to decide on the most appropriate antiepileptic drug treatment. Once two antiepileptic drugs have failed to control focal epilepsies, detection of epileptogenic lesions in epilepsy-dedicated MRI will help to identify if epilepsy surgery might be a good treatment alternative. With regards to cavernomas, ILEA recommendations suggest considering epilepsy surgery even after one antiepileptic drug failed to control the epilepsy. CT imaging in epilepsy is helpful in acute situations to exclude other underlying neurological conditions, which may trigger acute seizures such as stroke, intracranial haemorrhage, and encephalitis, among others. CT may help to detect calcifications as - for example in patients who suffer from cysticercosis - the underlying aetiology of epilepsy. However, in non-acute imaging of epilepsy, dedicated epilepsy MRI is first choice.

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