

CLINICAL BENEFIT OF 3 TESLA MAGNETIC RESONANCE IMAGING RESCANNING IN PATIENTS WITH FOCAL EPILEPSY AND NEGATIVE 1.5 TESLA MAGNETIC RESONANCE IMAGING

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ABSTRACT

Background: Magnetic resonance imaging is an essential tool in the pre-surgical evaluation of patients with drug-resistant epilepsy. **Objective:** Our aim was to assess the value of re-imaging patients with focal drug-resistant epilepsy. **Methods:** Thirty patients with negative or non-conclusive 1.5 Tesla magnetic resonance imaging were rescanned with 1.5T and 3T. All of them had previous 1.5 scans with no seizure protocol in a non-specialized center. Two neuroradiologists who were blinded to prior imaging results randomly reviewed the magnetic resonance images. Kappa score was used to assess the reliability. **Results:** Mean age of patients was 30 (SD \pm 11) years. The intra-observer agreement for the first radiologist was 0.74 for 1.5T and 0.71 for 3T. In the second radiologist it was 0.82 and 0.66, respectively. Three lesions (10%) were identified by general radiologists in non-specialized centers using a 1.5T standard protocol. In our center a consensus between two neuroradiologists using epilepsy protocol identified seven lesions (23%) using 1.5T and 10 (33%) using 3T ($p < 0.01$). In 28% of patients this additional information resulted in a change in clinical management. **Conclusions:** 3T magnetic resonance imaging rescanning improves the diagnostic yield in patients with focal epilepsy and previous negative 1.5T magnetic resonance imaging. Use of 3T magnetic resonance imaging, epilepsy protocols, and interpretation by experienced neuroradiologists is highly recommended. (REV INVES CLIN. 2018;68:112-8)

Key words: Epilepsy surgery. Lesional epilepsy. Magnetic resonance imaging. Partial epilepsy. Refractory epilepsy. 3 Tesla.

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INTRODUCTION

One of the main challenges of epilepsy surgery is precise localization of the epileptogenic zone, defined as the minimum amount of cortical tissue that must be resected to provide seizure freedom¹. Thirty² to 60%³ of patients with focal epilepsy have normal magnetic resonance imaging (MRI) and are denominated MRI-negative or non-lesional epilepsy cases. The presence of an MRI lesion and the reclassification of a patient with epilepsy from a “non-lesional” to a “lesional” category triples the likelihood of achieving seizure freedom after epilepsy surgery⁴; therefore, all efforts should be made to detect a lesion.

An MRI is the preferred imaging modality to detect structural lesions and determine a potential surgery. High-field MRIs provide an improved signal-to-noise ratio, which could theoretically result in higher image resolution, possibly providing better definition of subtle epileptogenic lesions missed on standard field MRIs⁵. Detection of structural lesions requires a high-strength field, but also a dedicated epilepsy protocol and meticulous examination of the images by the interpreting radiologist⁶, as well as post-processing analysis tools.

This is a prospective study assessing the value of re-imaging patients with drug-resistant focal epilepsy (DRFE) who were initially scanned with 1.5 Tesla (1.5T), using 3 Tesla (3T) MRI. Our hypothesis was that re-scanning patients in a specialized radiology center using an appropriate epilepsy protocol with a review by neuroradiologists would increase the possibility of detecting new lesions.

METHODS

This is a cross-sectional study performed at the Instituto de Alta Tecnología Médica (IATM) in Medellín, Colombia, between January 2012 and January 2014. The IATM is a center specialized in radiology. The Institutional Review Board of this institution approved the research protocol.

Patients

Patients with DRFE were recruited in two neurology clinics (Clínica Medellín and Hospital Universitario San Vicente Fundación in Medellín, Colombia) by two

neurologists specialized in epilepsy. The medical history of each patient was obtained from clinical charts, a standardized diagnostic interview, and neurological examination. Epilepsy type, seizure type, and epilepsy syndrome were classified according to recommendations of the International League Against Epilepsy (ILAE)⁷. Definition of drug-resistant epilepsy was determined by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies⁸.

Inclusion criteria

Patient inclusion criteria were as follows; (i) patient older than 14 years; (ii) clear diagnosis of DRFE by clinical history and electroencephalogram (EEG) findings; (iii) having normal or equivocal 1.5T MRI that failed to identify a relevant epileptogenic lesion; (iv) having been considered ineligible for surgery because of an inability to localize the potential epileptogenic zone; and (v) having already undergone a pre-surgical epilepsy evaluation, including at least a long-term video-EEG monitoring (120 hours or more). In some cases Positron Emission Tomography (PET), single-photon emission computerized tomography (SPECT), and psychiatric and neuropsychological evaluation were also part of the pre-surgical evaluation. Patients were asked to voluntarily participate in the study. A full explanation of the nature of the study was provided to them. Patients with previous epilepsy surgery or intracranial EEG evaluation, as well as patients with an implanted vagal nerve stimulator and absolute contraindications for undergoing MRI, were excluded.

Magnetic resonance imaging

All patients had a 1.5T scan prior to the study. This imaging was done without an epilepsy protocol in a non-specialized radiology center and was interpreted by a general radiologist. The entire sample of patients underwent a new 1.5T and 3T MRI in our center using an epilepsy protocol. Informed consent of participants was obtained before the MRIs.

All subjects were scanned on a Philips Ingenia MRI System with 3T and a Philips Achieva Nova Dual Series MRI System with 1.5T (Philips Medical Systems, Best, Netherlands) at the IATM, both with an 8-channel phased array sense head coil for signal reception. Sequences acquired for each patient in both machines included the following: Sagittal 3D

FLAIR (fluid attenuated inversion recovery); repetition time (RT) = 4,800, echo time (ET) = 344, NSA (number of signals averaged) = 2; voxel size = 1 x 1 x 1 mm; sagittal 3D T1-weighted, RT = 9.7, ET = 4.5; NSA = 2, voxel size = 0.8 x 0.8 x 0.8 mm; coronal T2-weighted drive, RT = 3,000, ET = 80, NSA = 2, voxel size = 0.7 x 1.0 mm; coronal T1-weighted IR (inversion recovery), RT = 1,400, ET = 15, NSA = 1, voxel size = 0.8 x 1.0 mm; Axial DWI-HR (diffusion-weighted imaging in high-resolution), RT = 4,382, ET = 126, NSA = 3, voxel size = 1.3 x 1.8 mm and sagittal 3D T2-weighted, RT = 2,200, ET = 262, NSA = 2, voxel size = 1.0 x 1.0 x 0.5 mm. With isovolumetric images the radiologists were able to assess areas suggestive of cortical thickening in directly orthogonal or perpendicular planes to rule out artifacts related to in-plane cortex. Intravenous contrast agents were not given. Total scanning time for the 1.5T and 3T MRI was about 80 minutes.

Image review

OsiriX (Geneva, Switzerland) version 4.1.1 was used by two neuroradiologists experienced in epilepsy imaging who independently and blinded assessed the scans. One neurologist summarized in a short sentence the clinical information of patients including age, gender, seizure semiology, and EEG information. Wording of the description was changed to strengthen the process of blinding. All scans were reviewed on a workstation running OsiriX software. The image sets were randomly coded with a random number. The two radiologists received the codes from the patients that they should read. The reviewers classified the MRI as normal or abnormal. An MRI was considered abnormal when a structural epileptogenic brain lesion was identified. Incidental lesions such as pituitary microadenomas or unspecific white matter hyperintensities were not considered significant. An MRI was considered abnormal when a focal lesion was identified with the standardized protocol such as mesial temporal sclerosis (MTS), focal cortical dysplasia (FCD), tumors, migration disorder, and others. Review by the two neuroradiologists was done with a timeframe of five days. Previous 1.5T scan reports were blinded to neuroradiologists. All the data were stored in a database called SQLite (<http://www.sqlite.org>). Finally, a team of neurologists and neurosurgeons determined if the new information resulted in a change in clinical management.

Statistical analysis

All analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL., USA). We used descriptive statistics to assess frequencies and distributions. We compared the final consensus reviews of 1.5T and 3T MRI. Inter-observer and intra-observer agreement was calculated using Kappa. We used a Chi-Square analysis to compare the final reading of MRIs from the IATM with previous 1.5T scan reports from non-specialized institutions. A p value < 0.05 was considered significant. All reliability estimates were presented with a 95% confidence interval (CI).

RESULTS

Thirty patients with DRFE were included. Sixteen (53%) were males; 25 (83%) were adults, and five (17%) were patients under the age of 18. The EEG and clinical focus was localized in the temporal lobe in 16 (53%), frontal in 10 (33%), insular in two (7%), and parieto-occipital in the other two (7%) cases (Table 1). The majority of patients (73%) had a psychiatric comorbidity, with depression being the most frequently reported (82%). All the patients were evaluated at least once for epilepsy surgery without success before the assessment in our center.

Structural lesions

Three lesions (10%) were identified by general radiologists in non-specialized centers using a 1.5T MRI standard protocol. The radiologic diagnoses were as follows: left parieto-occipital ulegyria, diffuse leukodystrophy, and a left temporal dysembryoplastic neuroepithelial tumor (DNET). These patients were not eligible for epilepsy surgery because the lesion detected in the MRI was discordant with the clinical and EEG findings. In these three patients, the new 1.5T and 3T MRIs with the special epilepsy protocol allowed a better anatomic definition of the pathologies; however, the new MRIs did not add any additional information and did not alter patient management in these cases. None of the patients have progressed to surgery at this time (Fig. 1).

In our center a consensus between the two neuroradiologists using an epilepsy protocol identified in total seven lesions (23%) using 1.5T, and 10 lesions (33%)

Table 1. Clinical characteristics of the patients

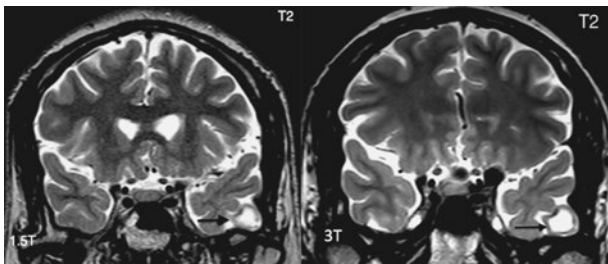
| Variable n = 30 | | N (%) | Mean (SD) |
|---------------------------------|----------------------|---------|-------------|
| Gender (male) | | 16 (53) | – |
| Age, years | | – | 30.2 (11.4) |
| Years of evolution | | – | 17.2 (11.4) |
| Frequency of seizures per month | | – | 25.3 (56.0) |
| Febrile seizures | | 5 (17) | – |
| Neonatal hypoxia | | 10 (33) | – |
| Family history of epilepsy | | 12 (40) | – |
| Developmental delay | | 14 (47) | – |
| Psychiatric comorbidity | Depression | 18 (60) | – |
| | Anxiety | 5 (17) | – |
| | Personality disorder | 2 (7) | – |
| Semiology and EEG foci | Temporal | 16 (53) | – |
| | Frontal | 10 (33) | – |
| | Parietal | 2 (7) | – |
| | Insula | 2 (7) | – |
| AEDs in the past | | – | 5.4 (1.8) |
| Actual number of AEDs | | – | 2.1 (0.7) |

AED: antiepileptic drug.

Figure 1. Comparison of imaging definition of a dysembryoplastic neuroepithelial tumor case in 1.5T and 3T magnetic resonance imaging.

T2-weighted coronal sequence showing a DNET with high signal and ‘bubbly appearance’. The lesion is better defined on 3T-MRI (on the right).

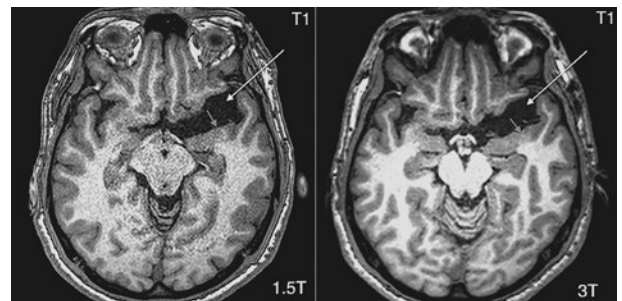
MRI: magnetic resonance imaging; DNET: dysembryoplastic neuroepithelial tumor.



using 3T MRI. The 1.5T and 3T scans identified the same lesions in seven cases. The 3T MRI identified three additional lesions. The four new lesions identified by a 1.5T MRI in our center were two cases of FCD, one heterotopia case, and one MTS case (Fig. 2). Two of the three additional lesions (67%) that were only identified by the 3T MRI were areas of FCD (Table 2). In total, half of FCD were located in the frontal lobe and the other half in the temporal lobe. One of the cases was detected only by one neuroradiologist as a small temporal pole encephalocele associated with FCD (Fig. 3). After the consensus meeting, the two

Figure 2. Comparison of imaging definition of a focal cortical dysplasia case in 1.5T and 3T magnetic resonance imaging. Axial 3D T1-weighted sequence showing a left temporal arachnoid cyst (white arrow) with an area of cortical dysplasia in the anterior temporal cortex (yellow arrow). The FCD was also detected on the new 1.5T-MRI (on the left). This finding is more clearly appreciated on 3T-MRI (on the right). The old 1.5T-MRI was interpreted as normal.

MRI: magnetic resonance imaging; FCD: focal cortical dysplasia.



neuroradiologists agreed with the diagnosis. According to the treating team, in two of these seven patients (28%) the additional information resulted in a change in clinical management. Finally, there was a significant difference ($p < 0.01$) between the abnormalities reported at non-specialized centers without epilepsy imaging protocol (3/30, 10%) and the results of our center (10/30, 33%).

Table 2. Magnetic resonance imaging findings of the sample

| Scan | New 1.5T | | Cons 1.5T | New 3T | | Cons 3T |
|-------------------|------------------------|------------------------|-----------|-----------------------|-----------------------|---------|
| Kappa | Intra-observer Kappa | | | Intra-observer Kappa | | |
| | R1 0.74 (p < 0.009) | R2 0.82 (p < 0.001) | | R1 0.71 (p < 0.01) | R2 0.66 (p < 0.07) | |
| Abnormal scans: n | 11 | 9 | 7 | 10 | 10 | 10 |
| Final diagnosis | | | | | | |
| MTS | 2 | 2 | 1 | 2 | 2 | 2 |
| FCD | 5 | 3 | 2 | 5 | 4 | 4 |
| Tumor (DNET) | 2 | 1 | 1 | 1 | 1 | 1 |
| Ulegyria | 1 | 1 | 1 | 1 | 1 | 1 |
| Heterotopia | | 1 | 1 | | 1 | 1 |
| Leukodystrophy | 1 | 1 | 1 | 1 | 1 | 1 |

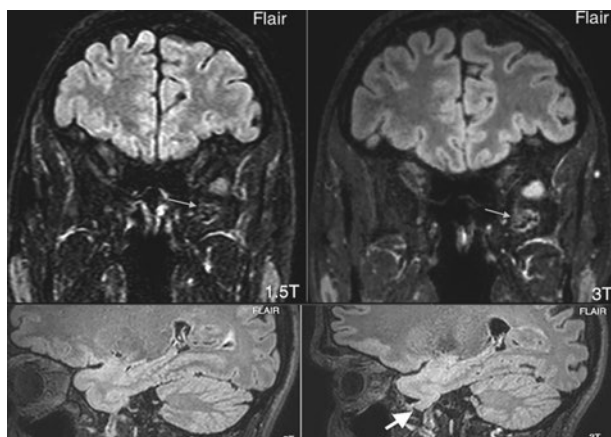
The new 1.5T magnetic resonance imaging consensus at the IATM detected seven lesions (23%) and the 3T magnetic resonance imaging detected 10 lesions (33%).

Cons: consensus; DNET: dysembryoplastic neuroepithelial tumor; FCD: focal cortical dysplasia; MTS: mesial temporal sclerosis; R1: radiologist one; R2: radiologist two.

Figure 3. Small encephalocele and focal cortical dysplasia.

At the top: a coronal 3D-FLAIR sequence showing a basal encephalocele on the left anterior temporal fossa with a small area of cortical dysplasia (white arrow). The finding was not detected in the new 1.5T-MRI (on the left), and is appreciated on the 3T-MRI (on the right). At the bottom: 3D-FLAIR technique showing comparative sagittal sequence of the normal right temporal lobe (on the left) and the abnormal left temporal lobe (on the right). The image shows a basal encephalocele on the left medial cranial fossa with protruding dysplastic cerebral cortex (white arrow). The imaging finding is consistent with the clinical and electrical suspicion in this patient.

MRI: magnetic resonance imaging; FLAIR: fluid attenuated inversion recovery.



Reliability

The intra-observer agreement for the first neuroradiologist was 0.74 for 1.5T and 0.71 for 3T. In the second neuroradiologist it was 0.82 and 0.66, respectively.

The inter-observer agreement was 0.76 for 1.5T (p < 0.001) and 0.77 for 3T (p < 0.001) (Table 2).

DISCUSSION

The most important finding in our study is that the use of 3T MRI with an adequate epilepsy imaging protocol and the interpretation of a neuroradiologist yielded relevant new findings in seven patients (26%) with DRFE who had previous 1.5T scan in other centers that had been reported as normal (7/27). Only by using a 1.5T MRI with epilepsy protocol were we able to detect a new lesion in 15% of cases (4/27).

Patients with established DRFE have increased risks of premature death, psychosocial dysfunction, and a reduced quality of life; therefore, they should be evaluated early for surgical treatment⁹. Because of potential negative outcomes in patients with DRFE, a major effort has to be made to identify a lesion, especially when epilepsy surgery has been considered⁴. Additionally, when the MRI is negative, further work-up is critical to help localize the epileptogenic zone¹⁰, and functional imaging (PET and SPECT) with or without invasive electroencephalographic monitoring is not always available and increases the costs considerably.

In the last three decades there has been a growing interest in the development of new techniques to identify structural lesions in the brain. The introduction of MRI for clinical use in the 1980s revolutionized the

diagnosis and surgical treatment of epilepsy. As a result of the improvement of technology, MRI has replaced CT in the work-up of patients with epilepsy^{11,12}. The increase of the magnetic field strength (0.5T, 1.0T, 1.5T, 3T, and 7T) will potentially provide more benefit for patients. All the technological changes have generated a substantial impact on the quality and definition of MRI imaging; for instance, doubling the field strength from 1.5T to 3T is estimated to increase the signal-to-noise ratio by a factor of 6-8, which potentially can increase the diagnostic yield of identifying lesions in surgical candidates with epilepsy¹³. Moreover, implantation of head coils¹⁴, the use of an epilepsy protocol including selected sequences, thin-slice thickness, and perpendicular orientation to the longitudinal axis of the hippocampal body¹⁵, as well as the reading by expert neuroradiologists, can also improve the diagnostic yield^{13,15}.

In our study, standard 1.5T MRI without epilepsy protocol in non-specialized centers failed to detect a focal lesion in 70% (7/10) of patients in whom 3T MRI detected a clear epileptogenic lesion. Similar findings were reported in previous studies. In a university hospital, 1.5T standard MRI did not detect lesions identified by four-coil phased-surface array 1.5T MRI in more than half the children (56%)¹⁶. In another prospective study performed in adults, von Oortzen, et al. demonstrated that in almost 60% of cases, conventional MRI without a neuroradiologist's standardized interpretation approach failed to detect structural lesions¹⁵.

In general, four (57%) of the seven new lesions detected in our study were areas of FCD. These results are similar to previous studies comparing 3T to 1.5T MRI, where 3T MRI was better in detecting areas of dysplasia¹⁷⁻¹⁹, as well as several other studies that compared phased array to standard head coil imaging^{13,20,21}. Our study shows that small areas of FCD may be missed with 1.5T MRI and the improved signal-to-noise of the 3T MRI studies, which can be translated in higher image resolution, results in better detection. The second type of new lesion detected in our study was hippocampal sclerosis, which is one of the most common radiological diagnoses in DRFE. This result corresponds well with previous studies by McBride, et al.²², von Oortzen, et al.¹⁵, and Winston, et al.¹⁷.

Additionally, our study shows a benefit in performing a 3T MRI in patients who already had a normal 1.5T

MRI. Three more lesions were identified using 3T MRI compared with 1.5T (10%). Similar percentages have been identified by other authors using 3T MRI compared with 1.5T MRI: Winston, et al. 5%¹⁷ and Nguyen, et al. 5%²³. Although it might be seen as a non-significant percentage, clinically it could be relevant because the decision to perform epilepsy surgery and the outcomes can be modified with the presence of a lesion²⁴. Therefore, some patients may benefit from re-scanning.

When assessing the ability of a test to be helpful to clinicians, it is important that its interpretation be precise. To estimate reliability of the MRI interpretations, we used the kappa coefficient of agreement to evaluate inter-observer and intra-observer variability. We have followed the classification system used by Landis and Koch²⁵, where agreement is quantified as slight (0.01-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80), and almost perfect (0.81-0.99). As expected, the agreement between observers for identification of MRI lesions on 1.5T and 3T was substantial (0.76 and 0.77). The second radiologist 3T intra-observer agreement was almost perfect (0.82), and all the other intra-observer agreements were likewise substantial. The clinical significance of a kappa value depends upon its context, and the values cannot be always compared between studies as it is dependent on disease prevalence; nonetheless, a recent study of FCD detection by MRI (kappa 1.5T: 0.83, kappa 3T: 1.0) reported higher values than were seen in our study¹⁹.

This study has some limitations. It is possible that because our readers were blinded to seizure semiology, lesions outside the lobe of interest may have been missed and lesions in the lobe of interest may be overcalled. This study is limited to findings on imaging; the final correlation of the lesion identified in MRI with the surgical outcomes is the most important. In the future, with a large sample size, it will be possible to make correlations with surgical outcomes. Finally, we believe that the differences between the studies from our center and the non-specialized center could be related with effects of higher field strength, a standardized epilepsy protocol, and an experienced reader, but we cannot rule out the possibility that some pressure and more expectations were given to the neuroradiologists to identify lesions during the study.

DECLARATION OF INTEREST

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