UPDATE IN RADIOLOGY

Structural magnetic resonance imaging in epilepsy

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Abstract  Magnetic resonance imaging is the main structural imaging in epilepsy. In patients with focal seizures, detection (and characterization) of a structural lesion consistent with electroclinical data allows therapeutic decisions without having to resort to other more expensive or invasive diagnostic procedures. The identification of some lesions may provide prognostic value, as in the case of Mesial Temporal Sclerosis (MTS) or may contribute to genetic counseling, as in the case of some Malformations of Cortical Development (MCD).

The aim of this paper is to review the current state of structural MRI techniques, propose a basic protocol of epilepsy and mention the indications for structural MRI and also, review the semiology of the main causes of epilepsy, with emphasis on MTS and MCD, by its highest frequency and by the special impact that MRI has shown in dealing with these entities.

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KEYWORDS
Magnetic resonance; Epilepsy; Mesial temporal sclerosis; Focal cortical dysplasia

PALABRAS CLAVE
Resonancia magnética; Epilepsia; Esclerosis temporal medial; Displasia cortical focal

Resonancia magnética estructural en la epilepsia

Resumen  La resonancia magnética (RM) estructural es la principal técnica de imagen en la epilepsia. En pacientes con crisis focales, detectar (y tipificar) una lesión estructural congruente con los datos electroclínicos permite tomar decisiones terapéuticas sin necesidad de acudir a otros medios diagnósticos más costosos o invasivos. La identificación de algunas lesiones aporta valor pronóstico, como en el caso de la esclerosis temporal medial (ETM), o puede ayudar al consejo genético, como en el caso de algunas alteraciones del desarrollo cortical (ADC).

El objetivo de este trabajo es revisar el estado actual de las técnicas de RM estructural y proponer un protocolo básico de epilepsia, así como mencionar las indicaciones para realizar una RM estructural. También se revisará la semiology de las principales lesiones que causan epilepsia, como la ETM y las ADC, por su mayor frecuencia y por el especial impacto que la RM estructural ha demostrado en su diagnóstico y tratamiento.

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Introduction

The study of the structure and function of the brain is an essential step for the diagnosis of patients with epilepsy. Structural magnetic resonance imaging (MRI) is the imaging technique that provides the most relevant information in the diagnostic and therapeutic process of these patients. However, this information largely depends on choosing an appropriate protocol able to provide suitable spatial resolution and signal-to-noise ratio, as well as optimal gray–white matter contrast. Any damage to the cortical gray matter of the cerebral hemispheres may cause epilepsy. Topic-specific literature should be consulted for more detailed information. Mesial temporal sclerosis (MTS) and focal cortical dysplasia (FCD) are the most common causes of refractory focal seizures, and they will therefore be discussed in detail.

MRI contributes to determine the possible focal origin of some seizures as well as the postoperative outcome—more favorable in conditions such as MTS, glial tumors or vascular malformations, these latter with a surgical success rate of 70–90%. Moreover, precise localization of a structural lesion relative to the functional area is indispensable to evaluate the surgical risk and the possibility for complete resection, which may be necessary to control seizures in many cases.

The International League Against Epilepsy recommends to perform an MRI in any patient with epilepsy, unless there is unequivocal evidence of idiopathic generalized or benign childhood epilepsy. It also recommends MRI in patients who develop seizures in adulthood or when seizures are difficult to control or have changed pattern. MRI is indicated when focal onset is suspected, even with previous negative studies. Periodical follow-up is required in lesions that could potentially grow or bleed, irrespective of the clinical manifestations. Some lesions can be undetected during the process of brain maturation, therefore once myelination is completed (24–30 months) the MRI study should be repeated.

Brain injuries should be ruled out after an initial seizure. The clinical manifestations and the patient’s age will determine the choice of imaging technique to be used. The primary cause of seizures in the neonate is hypoxia/ischemia; trauma and tumors in adults; and infarctions in the elderly. Although MRI is the technique of choice in patients with epilepsy, computed tomography (CT) has an important role in emergency situations given its higher availability, ease of retrieval, and its high sensitivity to detect acute hemorrhage, bone lesions or expanding lesions. Conversely, febrile seizures do not require imaging evaluation that should be reserved for patients younger than one year, when there are other neurologic abnormalities, clinical or electroencephalographic (EEG) suspicion of focal epilepsy.

Surgical treatment should always be considered in patients with refractory focal seizures—defined as seizures that cannot be satisfactorily controlled with two antiepileptic drugs (AEDs)—in order to control seizures and/or improve their quality of life. In these cases, MRI findings are particularly important because when they are consistent with the clinical and EEG findings, no further examinations will be required. In refractory seizures, MRI can detect 80% of the causative lesions in the temporal lobe and 60% in the frontal lobe. The postoperative outcome is clearly better when the structural lesion is detected. However, structural MRI has limitations secondary to its inability to detect some lesions and the potential poor correlation with clinical/EEG findings. In case of negative MRI, functional studies are recommended (photon emission tomography [PET] or ictal single-photon emission tomography [SPECT]), usually in combination with MRI to increase effectiveness. MR spectroscopy has proved useful in temporal lobe epilepsy (TLE), and although other advanced techniques such as diffusion and perfusion MRI seem promising, they need further validation. Lastly, individualized preoperative evaluation of the patient with epilepsy should be performed at a multidisciplinary Epilepsy Unit (neurologist, neurosurgeon, neuroradiologist, and neuropsychologist) where the most effective combination of diagnostic techniques for each particular case will be established.

Magnetic resonance protocol

MRI has changed the diagnosis of epilepsy not only radically, but also gradually, as the technological developments, in both hardware and software, have allowed for higher quality images. In epilepsy, the highest quality imaging is always recommended. Many studies have shown that field magnets <1.5 T are absolutely contraindicated and that standard MR imaging is inadequate as it reduces significantly the diagnostic accuracy.

The main objective of any structural study in patients with epilepsy is to achieve maximum tissue contrast between gray (GM) and white matter (WM) with high spatial resolution, in both the section (acquisition matrix) and the section thickness, which should range between 0.5 and 1 mm for 3D studies and 2 and 4 mm for 2D studies. At present, 1.5T systems are the most commonly used and if used with appropriate protocols they would solve most cases, except for some subtle malformations. 3T magnets are being increasingly used in epilepsy and they will probably replace 1.5T systems as they become more available in reference centers. Nonetheless, 1.5T magnets will continue to be used in a more standard setting but with special protocols that will allow for the detection of lesions in a more efficient manner and the possibility of consultation with epilepsy centers without having to repeat the MRI study, which would increase the cost of the process and unnecessary sedation in children.

T1 sequences should be obtained in 3D mode, with isotropic voxel of 1 mm and including the whole brain. Usually, inversion-recovery prepared gradient echo (GE) pulse sequences are used to increase GM/WM contrast (unlike spin echo [SE] sequences). They allow reconstruction in any plane without losing image quality, permitting, if necessary, volume rendering or curved reformations.

In the study of epilepsy, the hippocampus should always be evaluated in detail even when electroclinical data are not suggestive of temporal lobe epilepsy. Coronal sections perpendicular to the hippocampus should be obtained because they provide more information as well as high-resolution T2-weighted sequences with pixel <0.5mm, which means that for a field of view (FOV) of 240 mm the matrix should be ≥512. Three-dimensional sequences cannot be used to this end because the acquisition time required with the
current techniques would be too long. Instead, 2-D fast
SE sequences (also called turbo-SE, depending on the MR
system) should be used, with a 3 mm section thickness.
FLAIR sequences in the same planes should also be used
to detect contrast changes rather than to detect morpho-
logical or internal structural changes in the hippocampus.
Section resolution could be lower, with matrices of 256 and
a section thickness of 3–4 mm. FLAIR sequences are more
sensitive for the detection of small signal changes than T2
sequences, especially in areas adjacent to the cerebrospinal
fluid (Fig. 1).6

Since fast-SE technique has low sensitivity to mag-
netic susceptibility, lesions containing calcification or
hemosiderin such as small cavernomas7 may not be detected
(Fig. 2). For this reason, the study should be completed with
4–5 mm section axial T2* sequences, obtained with either
standard GE technique or echo-planar imaging (EPI), which
are faster and do not require high-resolution matrices.

Moreover, even if a temporal origin is highly suspected,
a whole-brain study using axial FLAIR sequences (al-
ternatively T2) should be performed to rule out small lesions
that directly cause the seizure, or lesions associated with an
hippocampal abnormality (dual pathology), with similar findings
on the coronal images. Imaging with multichannel coils is
always recommended because they increase the signal and
shorten imaging times, usually never less than 40 min. In
short, a basic epilepsy protocol includes 3D-T1, coronal T2
and FLAIR sequences and axial FLAIR and T2* sequences
(Table) (Fig. 3).

Postcontrast sequences are not indicated in a basic
epilepsy protocol, unless the clinical or imaging findings
make it necessary the evaluation of a specific lesion, partic-
ularly in case of suspected tumor.

3 T magnets have the advantage of increasing the signal-
to-noise ratio in an almost linear relationship to the field and
improving image contrast in T2. This results in an increase
in resolution and contrast, using acquisition times similar
to those used in a standard protocol. A field of 3 T also
allows for high-resolution matrices (of up to 1024) in T2
sequences, a decrease of section thickness to 1–2 mm in 2D
sequences8 and to 0.7 mm in 3D sequences (Fig. 4). In addi-
tion, the increased signal allows the acquisition of 3D-FLAIR
sequences that offer enhanced detection and delimitation of
small lesions. The use of 3 T systems for the study of patients
with refractory epilepsy is limited due to the scarce avail-
ability. Although the use of high-field MR systems is reserved
for individual patients in Epilepsy Units, they should be used
in any patient with refractory epilepsy with negative or non-
conclusive findings following appropriate protocols using a
1.5 T MR system.

Mesial temporal sclerosis

Hippocampal sclerosis is the most common feature of TLE,
and the most common cause of refractory epilepsy. His-
tologically, there is neuronal loss, mossy fiber synaptic
reorganization and astroglisis. The abnormalities are more
severe in certain areas of the hippocampus. In this respect,
the Sommer sector (CA1 field) is the most vulnerable and
is always impaired in MTS, with the most intense neuronal
loss. The Bratz sector (CA3 and CA4 fields) is less frequently
involved. The CA2 field or Spielmeyer sector is the most
resistant. This means that there is selective vulnerability,
not only in the brain but also within the hippocampus, and
that seizures play an important role in the development of
MTS.

Although the cause of MTS is not clearly established, in
fact, there is probably more than one cause, it seems to
be accepted that some type of insult during development
damages the hippocampus in predisposed individuals, who
develop MTS after the seizures begin. Complicated febrile
seizures and status epilepticus are associated with MTS in up to 80% of cases. Patients with status epilepticus have shown postictal abnormalities in the hippocampus and amygdala (Fig. 5).\(^9\) Postictal abnormalities of the hippocampus may be unilateral with postcontrast enhancement in the Sommer sector, reduction in the apparent diffusion coefficient, and, on follow-up imaging, may also show volume loss and mildly increased signal intensity on T2 sequences (Fig. 6). Many of these cases develop subsequent TLE.\(^10\) Although the presence of a previous insult in the hippocampus has not been clearly established, it seems probable that abnormal development of the hippocampus play an important}

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**Figure 2** T2-FSE (A) and T2-EPI (B) sequences. The small left parietal cavernoma is visible on T2-EPI but undetected on T2-FSE.

**Figure 3** Epilepsy protocol. Coronal 3D reformatted T1 weighted image (A), coronal T2 (B) and FLAIR images (C), axial FLAIR (D) and axial T2-EPI (E) sequences.
role since, although MTS may develop in adulthood, most patients report a precipitating event during childhood.

The most common MRI finding in MTS is hippocampal atrophy (90–95%) followed by abnormal signal, especially hypersignal on T2/FLAIR sequences (80–85%), and loss of internal structure (60–95%)\(^\text{11,12}\) (Fig. 7). However, technical factors have played a role in the frequency of findings because as sequences and especially MR magnets have improved, more subtle changes in signal and internal structure without significant loss of hippocampal volume are being detected.\(^\text{13,14}\) This is typical of endfolium sclerosis, a histological subtype of MTS where the lesions are limited to the CA3 and CA4 fields. In this pattern, the only finding could be the increased signal in the central region of the hippocampus on T2 or FLAIR sequences.\(^\text{15}\) In doubtful cases, the use of 3 T MR systems increases the sensitivity (Fig. 8). In addition, when the volume loss is not conspicuous, loss of digitations in the head of the hippocampus may be indicative of focal atrophy. MRI-based volumetric measurements of the hippocampus may be useful in the research field and in doubtful cases especially when bilateral MTS is suspected, where visual analysis is more limited.\(^\text{16}\)

In addition to the hippocampus, other structures of the limbic system may be involved, leading to secondary findings. Dilatation of the ipsilateral temporal horn is common, although it has no value as isolated finding because asymmetries of this structure also occur in healthy subjects. Occasionally, the amygdala can demonstrate hyperintensity, probably reflecting similar abnormalities to those of the hippocampus. Loss of volume of other limbic structures such as
the entorhinal cortex, fornix or the ipsilateral mammillary body is less common, but these findings are usually associated with conspicuous hippocampal changes, and their diagnostic value is limited. According to autopsy studies, the contralateral hippocampus frequently shows histological changes, but MRI findings do not exceed 20%.

Dual pathology—that is, MTS in association with another lesion—has been described in up to 15% of cases. Dual pathology is most commonly seen in patients with disorders of the cortical development disorders (DCD). However, the frequency and nature of some anomalies associated with MTS remains unclear. Up to 65% of patients with MTS had subtle signal abnormalities in the WM of the temporal lobe, visible as poorly defined high signal on FLAIR sequences, sometimes with a blurred cortical–subcortical junction (Fig. 9). Some histological studies suggest that only changes in myelination of the temporal lobe occur, while others have described type I FCD. It remains unclear whether these changes play a role in the development of MTS or MTS is the consequence of these changes, as it alters...
temporal lobe maturation. In any case, it is important to detect the structural abnormalities associated with MTS, because, regardless of the etiologic factors, the outcome for selective amygdalohippocampectomy is worse in patients with dual pathology. Resection of both lesions is, when possible, recommended.

Several subtypes of MTS have been described, which are being increasingly identified as the quality of MRI studies improves. The most common type is "unilateral diffuse hippocampal sclerosis" , which shows the typical MRI findings. In "unilateral anterior sclerosis", only the head of the hippocampus is involved. This is a less common cause of refractory epilepsy that tends to develop later in life than the unilateral diffuse type (Fig. 10). Seizures in "temporo-occipital epilepsy with MTS" may arise exclusively from the occipital lobe, but usually they spread to the temporal or frontal lobe. Association of an occipital focus with MTS is regarded as secondary MTS that results from the spread of epileptogenic activity to the temporal lobe. "Diffuse bilateral sclerosis" (Fig. 10) has been described in 10% of patients with refractory TLE. Seizures usually start earlier in life and secondary generalization is more common than in unilateral sclerosis. This suggests that specific lesions such as meningoencephalitis or toxic-metabolic encephalopathy may be the cause of generalized seizures. Patients with diffuse bilateral sclerosis show more memory impairment and other cognitive abnormalities. In these patients, the surgical outcome is not as good and the cognitive sequelae are usually more severe, because of the damage in the contralateral hippocampus.

About 70% of patients with typical MTS are seizure-free after surgery. Studies using several imaging modalities have shown that in case of typical MTS the presence of hippocampal atrophy is the major predictive factor of surgical success, but optimal outcome is achieved when all the modalities provide similar findings. Surgery is not contraindicated in contralateral atrophy, but the outcome is less favorable and the neuropsychological sequelae more severe. Amygdalohippocampectomy is not sufficient in temporo-occipital epilepsy, as in dual pathology, where lobectomy is recommended.

Disorders of cortical development

DCD are common in patients with epilepsy, particularly those whose epilepsy develops in childhood. They result from
disruption of the different stages of cortical development that involves three consecutive but not isolated events: proliferation/apoptosis of neuroblasts within the germinial matrix, radial and tangential migration of neuroblasts from the germinial matrix towards the periphery of the brain, layered organization of the cortex with formation of a network of synaptic connections. Overall, about 15% of patients with DCD have refractory seizures and surgery may help to control them in some cases.

The study protocol of DCD is in general more comprehensive than that used in the rest of causative disorders of epilepsy. In addition to the standard 3D-T1 sequences, at present, 3D-T2 and 3D-FLAIR sequences can assess very accurately small abnormalities in the cortical-subcortical junction and in the adjacent WB. Three-dimensional sequences, the new phased array multichannel coils and high-field magnets have significantly improved the efficacy of MRI in DCD.

In the neonate, 3D-T1 and T2 are the most useful sequences. FLAIR sequences, essential in adults, are of limited value because the scarce myelination makes them less sensitive to detect small lesions. Continued myelination causes a frank reversal of the WM hypointensity on T1 and hyperintensity on T2 sequences, producing the adult intensity pattern at 24–30 months. Up to 6 months, T2 sequences are more reliable, and T1 sequences between 12 and 24 months. Between 6 and 12 months, reliability of MRI is particularly low, early imaging is thus recommended, and if performed in infants older than three months, it should be repeated after 24 months.

Medical treatment should begin as soon as the DCD is diagnosed and MRI may help determine the optimal treatment, for example, vigabatrin for tuberous sclerosis with West syndrome. When diffuse abnormalities are detected, surgical treatment is not very effective—in contrast with focal lesions such as FCD—because incomplete resections is the major predictor of poor outcome in the control of seizures. Determining the type of disorder is of particular help for prognosis and genetic counseling. The degree of impairment usually correlates with the extent of the malformation; for instance, in band heterotopia the thickness of the band correlates with the degree of psychomotor impairment and with treatment failure. In schizencephaly, cleft size and bilaterality determine the outcome. Some MRI findings can lead to the molecular defect diagnosis causing the DCD. In this respect, mutations of the LIS1 gene are responsible for parieto-occipital pachygyria (frontal pachygyria is probably secondary to mutations of the DCX gene), and mutations of the FLM gene are responsible for periventricular heterotopia, which determines genetic counseling.

There are three groups of DCD according to the Barkovich classification that are based on the stage of cortical development primarily involved. Group I (proliferation) includes microcephaly and hemimegalencephaly, type II FCD, tuberous sclerosis, and tumors such as dysembryoplastic neuroepithelial tumor (DNT) and gangliogioma/gangliocytoma. Group II (migration) includes lissencephaly, cobblestone cortex and heterotopias. Group III (organization) includes polimicrogyria, schizencephaly and type I FCD (Table 1).

The Barkovich classification, based on embryologic criteria, is the most commonly used. Although this classification remains fully in force, some novelties are attracting increasing attention, especially in FCD, not only because FCD are the most common disorders in patients with refractory focal seizures, but also because surgical treatment is proving useful in many cases.

**Focal cortical dysplasia**

FCD encompass a spectrum of disorders ranging from mild to severe cortical abnormalities, sometimes in association with other lesions including MT or tumors with low proliferative potential such as DNT or neuroglial tumors. Detection as well as characterization of DCF is crucial because the surgical treatment and prognosis change depending on the type of lesion.
Typical signs of FCD are abnormal gyral pattern, cortical thickening, indistinct junction between GM-WM and signal changes of WM, usually without expansion effect. 1.5 T MRI systems may not detect some FCD. In fact, one of the main applications of 3 T system is the diagnosis of FCD. One of the most relevant studies conducted in 45 patients with histologically confirmed lesions revealed that 3 T MR systems may detect up to 40% more lesions compared to standard 1.5 T, motivating a change in clinical management in more than 35% of cases (Fig. 11).

The most common histological findings of FCD are disorganized cortical architecture (dyslamination) (92%), increased number of molecular layer neurons (62%), increased neuron size (cytomegaly) (62%), dysplastic neurons and balloon cells (37%). Other findings are less common. Grading of FCD is based on the severity of the abnormalities: the mildest degree is the architectural dysplasia with dyslamination. A more severe degree is the cytoarchitectural dysplasia with cytomegaly neurons. Taylor's dysplasia is considered the most severe abnormality, with dysplastic neurons with or without balloon cells. Palmini proposes a classification of cortical dysplasia based on these histological features: type I refers to lesions with dyslamination (type Ia or architectural) or cytomegaly (type Ib or cytoarchitectural), and type II (the Taylor-type) refers to the presence of dysmorphic neurons (type IIa) with balloon cells (IIb). Much of the interest in differentiating these two histological types arises from recent publications that suggest the possibility of characterization using MRI and, particularly, the fact that their different clinicopathologic features are associated with varied surgical success. Both types have characteristic imaging findings. Abnormalities in FCD type I (Fig. 12) may extend to one or multiple lobes and are frequently associated with volume loss of WM, without thickening or abnormal cortical pattern, and without cortical signal changes. The subcortical WM usually exhibits a moderately increased signal on FLAIR sequences and, to a lesser degree, on T2 images, with blurring at the GM-WM junction. FCD type I are more difficult to detect than type II by MRI because of the minor cortical changes and subtle WM abnormalities. The volume loss and association with perinatal events suggest the presence of possible destructive lesions during the late stages of brain development. FCD type I is most frequently encountered in the temporal lobe and in association with MTS, and it is thus considered as dual pathology. FCD type I is associated with a clearly less favorable surgical outcome than FCD type II probably due to its higher extent and worse delimitation.

FCD type II (Fig. 11D) shows a more archetypal semiology with thickening and/or abnormal gyral pattern and, frequently, cortical signal changes. There is poor correlation between cortical thickening on MRI and histological findings. This is probably due more to an abnormal signal from the juxta cortical WM—which simulates a thickened cortex particularly on FLAIR sequences (“cortical pseudo-thickening”)—rather than to true cortical thickening. For this reason, cortical thickening should be carefully evaluated with T1 and T2 sequences. WM abnormalities are usually more conspicuous, clearly visible on FLAIR sequences in most cases, and represent one of the factors that allow better detection by MRI. Abnormal WM signal usually involves the entire thickness, from the cortex towards the ventricle (transmantle dysplasia), like the vertex of a triangle located in the ventricle. This sign may be very useful in the differential diagnosis with tumor lesions and is almost exclusively found in FCD type II. Unlike type I lesions, type II lesions occur more commonly in the frontal lobe.
Association of FCD with tumors such as DNT and ganglioglioma should be suspected in the presence of cysts or nodules. Association with calcifications is more common in gangliogliomas. Contrast-enhanced T1 imaging is recommended when any of these findings is detected. The presence of enhancement is very suggestive of tumors.

FCD are better visualized during the first month of life, that is, when the peripheral regions of the cerebral hemispheres are not myelinated yet. There is more contrast of the dysplastic cortex and subcortical WM with the normal brain (with hypointensity on T1 and hyperintensity on T2 sequences, unlike adult brain). In adult brain the lesion is much less conspicuous. Additionally, ischemic lesions in the neonate are a common cause of epilepsy and are clearly visible on diffusion-weighted images during acute phases. For this reason, an MRI epilepsy protocol with diffusion sequences is recommended in neonates with seizures.

Conclusion

Structural MRI is an essential part of the diagnostic process of epilepsy and involves a specific protocol with high spatial and contrast resolution. Most lesions causing refractory epilepsy can be visualized on structural MRI and its detection is crucial for subsequent diagnostic and therapeutic planning and, in the event of a negative MR, one must always consider the possibility of increasing image quality. MTS and DCD, especially FCD, are common causes of refractory epilepsy exhibiting a characteristic semiology. Understanding of the different manifestation on structural MR images is thus very important, as well as the possible associations in dual pathology of MTS or between FCD and neuroglial tumors. Nonetheless, some lesions such as FCD type I may have a negative or non-conclusive structural study or, on some occasions, incidental lesions unrelated to epilepsy may
be discovered. Correlation with electro-clinical data is thus essential and, in non-conclusive cases, functional studies, such MRI coregistered PET or ictal SPECT, should also be considered. However, these examinations, as with invasive electrodes, must be assessed in dedicated epilepsy units, with a multidisciplinary approach.

Conflict of interest

The author declares not having any conflict of interest.

References


