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INVITED REVIEW / DAVETLİ DERLEME

Neuroimaging in Focal Epilepsies: An Update

Fokal Epilepsilerde Nörolojik Görüntüleme: Güncelleme


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Summary

Epilepsy is a common neurologic disorder with diverse etiologies. Appropriate MRI investigation has an important role in the assessment of epilepsy. Specific protocols are required for recognition of epileptogenic lesions, particularly for recognition of subtle lesions. In patients with refractory epilepsy and "normal MRI," multimodal imaging techniques are crucial in the definition of epilepsy etiology, including those that combine metabolic and functional investigation, such as fluorodeoxyglucose positron emission tomography (FDG-PET), single-photon-emission computed tomography (SPECT), diffusion MRI and magnetic resonance spectroscopy (MRS). Familiarity with various protocols of imaging studies is required for optimized investigation of seizure etiology. Main features found in MRIs of patients with focal epilepsies are discussed in the present review, as are alternative protocols and techniques of imaging that may optimize neuroimaging investigation in patients with epilepsy. The findings described have a direct impact on treatment and prognosis counseling of patients with focal epilepsies.

Keywords: Focal epilepsies; neuroimaging.

Özet

Epilepsi, çeşitli etiyolojileri olan yaygın bir nörolojik rahatsızlıktır. Epilepsi değerlendirmesinde uygun manyetik rezonans görüntüleme (MRG) incelemeleri önemli bir role sahiptir. Epileptojenik lezyonların, özellikle güç alıgılanılan lezyonların teşhisi için spesifik protokollere ihtiyaç vardır. Dirençli epilepsisi olan ve "normal MRG" sonuçlarına sahip hastalarda florodeoksiglikoz-pozitron emsiyon tomografisi (FG-PET), tek föton emisyon bilgisayarlı tomografi (SPECT), difüzyon MRG ve manyetik rezonans spektroskopisi (MRS) gibi metabolik ve fonksiyonel incelemeleri de birleştiren multimodal görüntüleme yöntemleri epilepsi etiyolojisini tanımlamada önem taşımaktadır. Görüntüleme yöntemlerinin farklı protokollerine aşina olmak nöbet etiyolojisinin optimize incelemesi açısından gereklidir. Biz bu çalışmada, fokal epilepsisi olan hastaların MRG incelemesinde bulunan başlıca özellikleri tartışacağız. Ayrıca, epilepsisi olan hastaların nörolojik görüntüleme ile yapılan incelemelerini en uygun hale getirebilecek farklı görüntüleme yöntemleri ve alternatif protokolleri de tartışacağız. Burada tanımlanan bulguların, fokal epilepsisi olan hastaların tedavisi ve prognoz danışmanlığı üzerine doğrudan bir etkisi olacaktır.

Anahtar sözcükler: Fokal epilepsi; nörolojik görüntüleme.

Introduction

Epilepsy is one of the most prevalent chronic neurological disorders affecting approximately 50 million people worldwide[1] and is characterized by the occurrence of spontaneous recurrent seizures.[2]

Many patients respond well to optimized anti-epileptic drugs (AEDs) treatment; however, seizure freedom is not always reached. Uncontrolled epilepsy markedly affects patients' quality of life and has devastating effects on cognitive function. Furthermore, it also increases the risks of sudden death.[3] At least 30% of patients are refractory to AEDs or do not tolerate medications due to side- effects.[4] Surgery should be considered as an important option for pharmaco-resistant epilepsy. To that end, the role of neuroimaging, mainly magnetic resonance imaging (MRI), becomes indispensable, since it is a non-invasive tool that allows us to identify lesions involved in epilepsy. It also allows us to monitor disease progression.[5]

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This paper will review the role of neuroimaging in epilepsy, discussing the main features found in MRI of patients with focal epilepsies.

Reasons for Performing MRI in Patients With Epilepsy

When a first seizure occurs, it often refers to a bilateral convulsive seizure. The probability of recurrence is variable, with studies showing that the risk of recurrence after a first tonic-clonic seizure is around 50% in the next year or two. [6,7] How and when a patient with a first seizure should be imaged depends on scanner availability and the suspected cause of the seizure.[8]

In patients with well-defined genetic epilepsies or age related epilepsies (e.g. juvenile myoclonic epilepsy) the need of a MRI may be argued. However, if there is suspicion of a structural cause, an MRI should always be performed. In the setting of an acute seizure in older patients the role of neuroimaging is essential to rule out structural lesions.[9]

By helping defining the etiology of epilepsy, MRI becomes an important tool for prognostic counseling and defining treatment strategy. We can, also, use MRI to monitor progression of lesions. DTI, 3D reconstructions and co-registrations are important tools in surgical planning (Figure 1).

In the research field, MRI allows us to better understand the pathophysiology of epilepsy.[5]

How to Perform an MRI

In the setting of new onset epilepsy, clinical evaluation, electroencephalographic findings and neuroimaging should be considered together when defining the probable etiology of epilepsy. Among these methods, MRI is the only one that may show the etiology of seizures. The epileptogenic lesion may be detected using routine MRI protocols. However, routine MRIs often miss smaller or subtle lesions and are considered normal. Therefore, in these cases, an optimized epilepsy protocol with adequate spatial resolution and multiplanar reformatting is essential9 (Figure 2).

Epilepsy protocols should be chosen depending on the clinical hypothesis. Suggested protocols are summarized in Tables 1, 2.

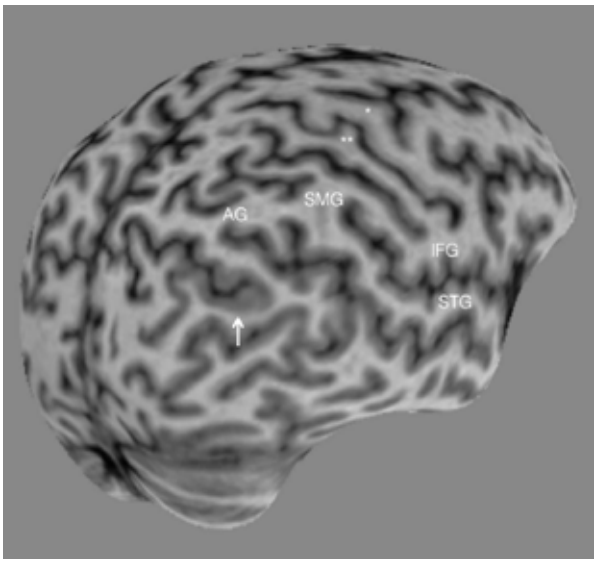

Fig. 1. Curvilinear reconstruction showing right parietal cortical thickness (arrow) and its correlation with adjacent gyrus. GA: Angular gyrus; SMG: Supramarginal gyrus; IFG: Inferior frontal gyrus; STG: Superior temporal gyrus; *precentral gyrus; ** Postcentral gyrus.

In this context, MRI epilepsy protocols should include a 3D, T1-weighted volumetric acquisitions with isotropic voxel of 1 or 1.5 mm in order to reconstruct images in any plane (Figure 3), as well as, FLAIR 3D (Fluid Attenuation Inversion Recovery), T1-weighted IR (inversion recovery) and DIR 3D (Double Inversion Recovery) sequences should be added, mainly when cortical dysplasia is considered. For mesial temporal lobe epilepsy (MTLE), other sequences are also important: thin coronal MRI slices, perpendicular to the long axis of the hippocampus (Figure 2), T2-weighted, FLAIR and T1-weighted IR.

In addition to the technical aspects of MRI acquisition, the experience of the examiner and a clinical/encephalographic correlation are essential when searching for subtle epileptogenic lesions.[8,9]

Most Frequent MRI Findings According to the Clinical Syndromes

Temporal Lobe Epilepsy (TLE)

TLE is the most frequent form of focal epilepsy in adults. [10] One third of patients are pharmaco-resistant. TLE is frequently associated with structural abnormalities, but other forms of non-lesional TLEs have been described, such as some forms of familial temporal lobe epilepsy (Figure 4).[11-13]

Table 1. Suggestion of MRI hippocampal protocol

Coronal images perpendicular to the long axis of the hippocampus

1) T2WI multiecho (3- mm-thick, no gap, voxel size = 0.89x1x3 mm, TR = 3300 ms, TE = 30/60/90/120/150 ms, matrix = 200x180, FOV = 180x180, TSE factor = 5; EPI factor = 5, flip angle = 90°);
2) T1WI inversion recovery (3-mm-thick, no gap, voxel size = 0.75x0.75x3 mm,TR = 3550 ms,TE = 15 ms,TI = 400ms,matrix = 240x229, FOV = 180x180, TSE factor = 7),
3) FLAIR (fat-suppressed = spectral-attenuated inversion recovery, fat-suppressed power = 1, four-mm-thick, section gap = 1 mm, voxel size = 0.89x1.1x2.4 mm,TR = 12,000 ms,TE = 140 ms,TI = 2850 ms, matrix = 180x440, FOV = 200x200).

Axial images parallel to the long axis of the hippocampus

1) FLAIR (fat-suppressed = spectral-attenuated inversion recovery, fat-suppressed power = 1, four-mm-thick, section gap = 1 mm, voxel size = 0.89x1.1x2.4 mm, TR = 12000 ms, TE = 140ms, TI = 2850 ms, matrix = 224x160, FOV = 200x200).
2) T1WI volume: isotropic voxels of 1 mm, acquired in the sagittal plane (1-mm-thick, no gap, flip angle = 8°, TR = 7.0 ms, TE = 3.2ms, matrix = 240x240, FOV = 240x240).
3) T2WI volume: isotropic voxels of 1.5 mm, acquired in the sagittal plane (no gap, TR = 1800 ms, TE = 340 ms, matrix = 140x140, FOV = 230x230, TSE factor = 120; flip angle = 90°; geometry-corrected).
4) DTI (Diffusion Tensor Imaging) – Spin echo single shot planar imaging, voxel size = 2x2x2 mm, matrix = 256x256, TE/TR 61/8500 ms, gradient directions = 32.

Sagittal images parallel to the long axis of hippocampus

1) T2WI 3D: no gap, FOV = 230x230, voxel size = 1,5x1,5x1,5 mm, TR = 1800 ms, TE shortest.
2) FLAIR 3D (fat-suppressed = spectral-attenuated inversion recovery): FOV: 250x250, voxel size = 1,2x1,2x1,0 mm, TR = 4800 ms, TE shortest, TI = 1650 ms.

Table 2. Suggestion of MRI focal cortical dysplasia protocol

1) T1WI volume: isotropic voxels of 1 mm, acquired in the sagittal plane (1-mm-thick, no gap, flip angle = 8°, TR = 7.0 ms, TE = 3.2ms, matrix = 240x240, FOV = 240x240).
2) FLAIR 3D, acquired in the sagittal plane (fat-suppressed = spectral-attenuated inversion recovery): FOV: 250 x 250, voxel size = 1,2x1,2x1,0 mm, TR = 4800 ms, TE shortest, TI = 1650 ms
3) FLAIR (fat-suppressed = spectral-attenuated inversion recovery, fat-suppressed power = 1, four-mm-thick, section gap = 1 mm, voxel size = 0.89x1.1x2.4 mm, TR = 12000ms, TE = 140ms, TI = 2850 ms, matrix = 224x160, FOV = 200x200).
4) T2WI 3D, acquired in the sagittal plane: no gap, FOV = 230x230, voxel size = 1,5x1,5x1,5 mm, TR = 1800 ms, TE shortest.
5) T1WI inversion recovery (3-mm-thick, no gap, voxel size = 0.75x0.75x3 mm,TR = 3550ms,TE = 15ms,TI = 400ms,matrix = 240x229, FOV = 180x180, TSE factor = 7),
6) DIR (double inversion recovery), acquired in th axial plane perpendicular to the long axis of the hippocampus: voxel size = 1.2x1.2x0.6 mm, TR = 5500 ms, TE shortest, TI 2550 ms.
7) DTI (Diffusion Tensor Imaging) – Spin echo single shot planar imaging, voxel size = 2x2x2 mm, matrix = 256x256, TE/TR 61/8500 ms, gradient directions = 32.

MTLE with Hippocampal Sclerosis (HS)

In MTLE, electroencephalographic findings, clinical history and neuroimaging findings are important to define the diagnosis. Although there are others etiologies that cause ELT, HS is the most common pathological substrate. MTLE with HS is often associated with a precipitating injury such as complex febrile seizures, birth trauma, meningitis or head injury that happens in early life.[14] A latent period of several years may precede dyscognitive seizures (previously known as complex partial seizures).[15]

The MRI findings often show volumetric reduction of hippocampal formation (atrophy), increased signal intensity in T2-weighted sequences, loss of normal hippocampal architecture with loss of hippocampal head digitation (Figure 5) better identified in thin coronal MRI slices, perpendicular to the axis of the hippocampus.[16]

Secondary MRI findings of HS include: atrophy of structures of the limbic system, such as amygdala, ipsilateral mammillary body, entorhinal cortex, ipsilateral fornix, posterior thalamus, cingulate gyrus and contralateral cerebellum.[17,18] Atrophy-signal alterations of the contralateral hippo-

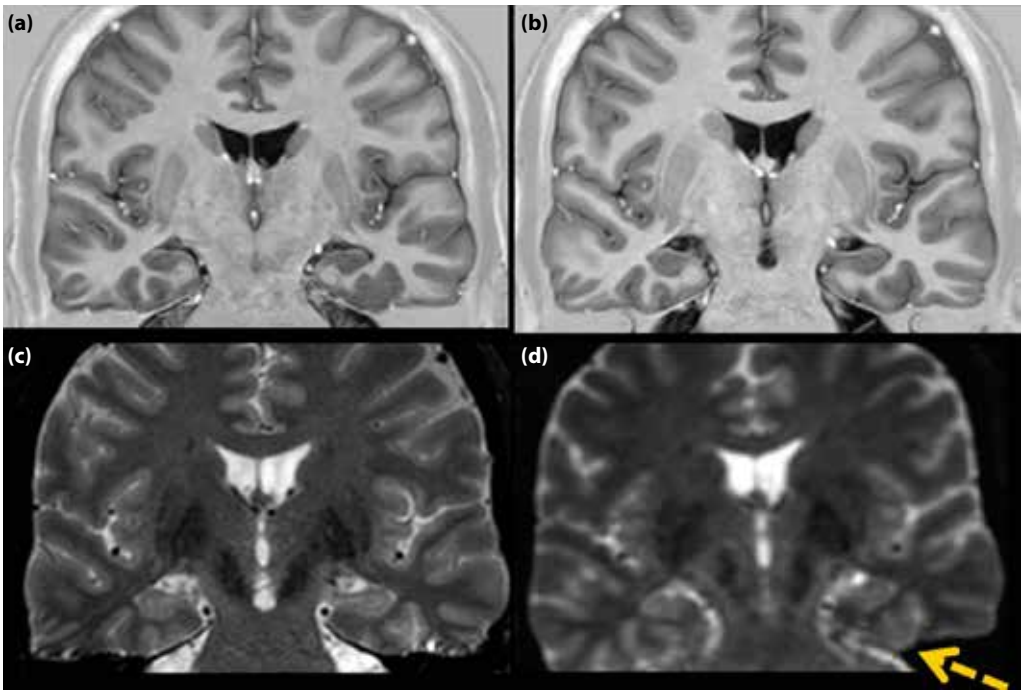

Fig. 2. **(a-d)** T1 IR and T2WI MRI sequences showing subtle FCD in the left collateral sulcus.

campus and dilation of the ipsilateral temporal horn of the lateral ventricle can also be present.[19]

Although about 10 - 20% of patients have symmetrical bilateral HS, the comparison between both hippocampi is also an important tool to detect asymmetries (Margerison and Corsellis, 1966) bearing in mind, that sometimes, mild hippocampal atrophy with or without increased T2/FLAIR signal may be found in MRI scans in older patients related to aging.

MTLE with Normal MRI

Some patients with MTLE may have an MRI read as normal.

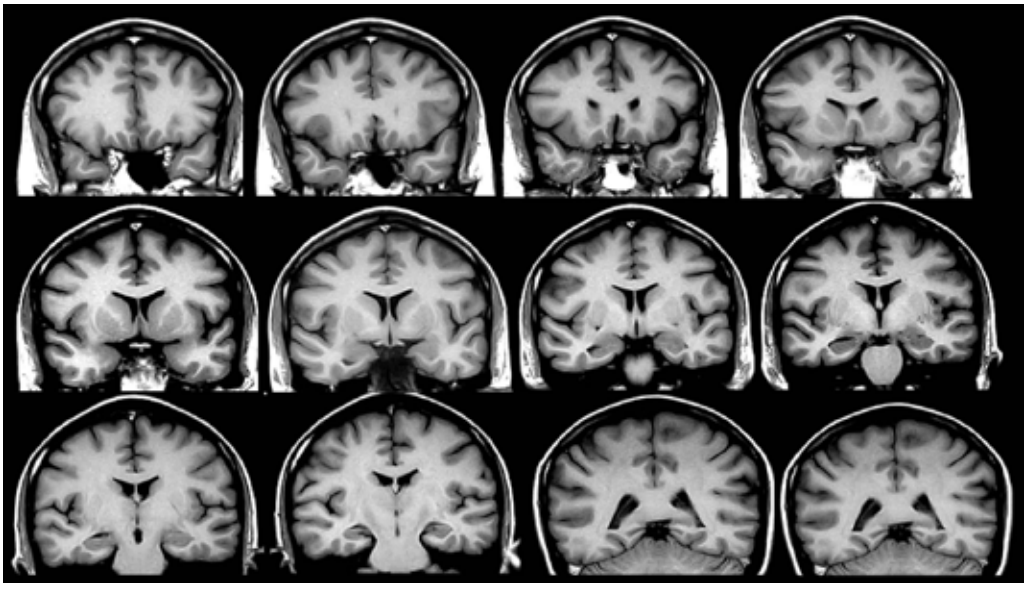

Fig. 3. Normal 3D T1 WI MRI in coronal slices volumetric acquisitions.

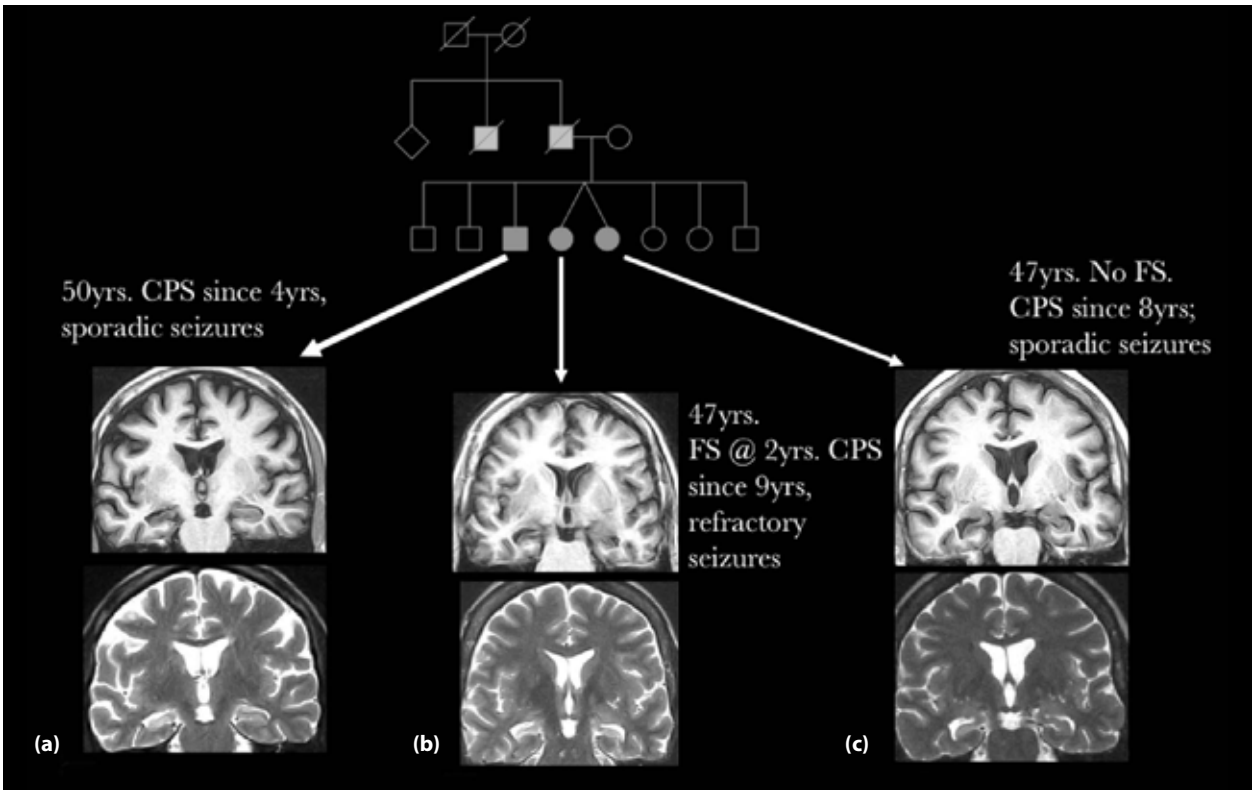

Fig. 4. T1 and T2 MRI sequences in coronal slices showing familiar MTLE with right HS **(a, c)** and bilateral HS **(b)**.

[20,21] In these cases, advanced techniques of imaging including magnetic resonance spectroscopy (MRS), interictal FDG-PET, ictal SPECT (Figure 9), quantitative analysis of hippocampus formation such as volumetry and relaxometry,[22-25] can be useful tools for diagnostic and lateralization of seizure onset (Figure 6).

In refractory epilepsies, when a focal lesion is found, surgery is the best treatment. In these cases, appropriate MRI protocols and expertise in MRI of epilepsy are required. On the other hand, when no lesion is found, the area of resection has to be defined by other tools (e.g. EEG, PET, SPECT); however, a less optimal surgical outcome may be expected.[15]

Although the HS is the most common structural abnormality found in TLE, there are many other causes that may lead to TLE such as tumors (Figure 7), gliosis, vascular malformations, congenital cysts and a wide variety of malformation of cortical development, which may lead to similar clinical findings to those of MTLE due to HS (Figure 12).[26]

Extra-Temporal Lobe Epilepsy

Focal lesions outside the temporal lobe are frequently resistant to clinical treatment, with up to 25-30% of patients

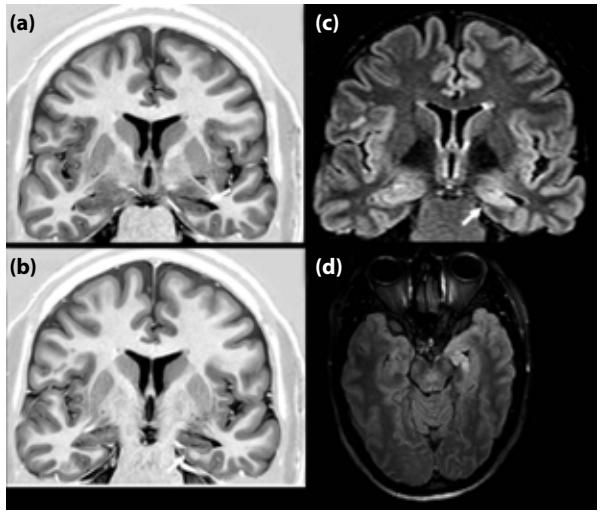

Fig. 5. **(a, b)** T1 IR and **(c, d)** FLAIR MRI sequences showing left HS, characterized by volumetric reduction of hippocampus, increased signal intensity and loss normal architecture.

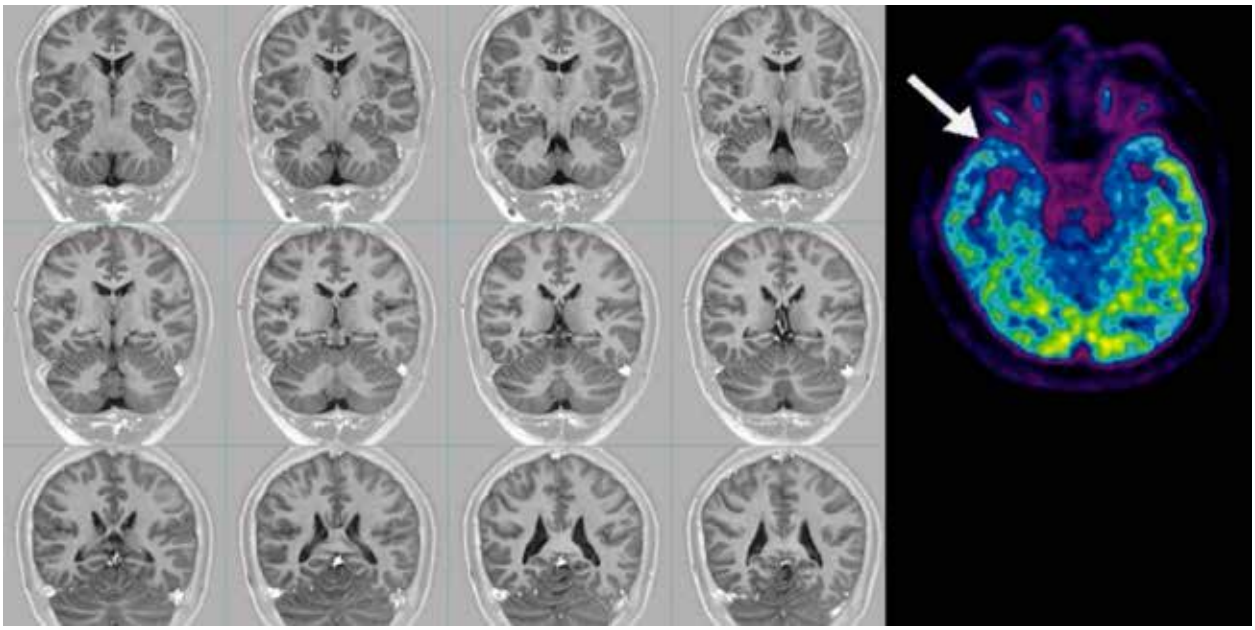

Fig. 6. T1 IR MRI sequence with normal findings and FDG-PET showing hypometabolism in the temporal lobe.

being refractory to AEDs. Clinical presentation depends on the exact location of the abnormality. Defining the focal epileptogenic zone is of paramount importance, since good surgical outcome depends on complete resection of the lesion displayed on MRI and the surrounding "MRI-invisible" epileptogenic tissue.[27-29]

In extra-temporal lesions, the MRI investigation has its own features. MRI may be unremarkable even in malformations of cortical development. In these cases, multimodal techniques of imaging can be useful for localizing suspected lesions. Among the multimodal imaging, the interictal FDG-PET, ictal SPECT, ictal/interictal subtraction of SPECT scans, PET/MRI co-registration, multiplanar reconstruction and curvilinear reformatting represent noninvasive methods to evaluate patients with focal seizures (Figure 8).[30-32]

The most common lesions causing neocortical epilepsies are: low grade tumors, malformations of cortical development, posttraumatic and postischemic lesions, inflammatory infectious scars, cavernous angioma and arteriovenous malformations.

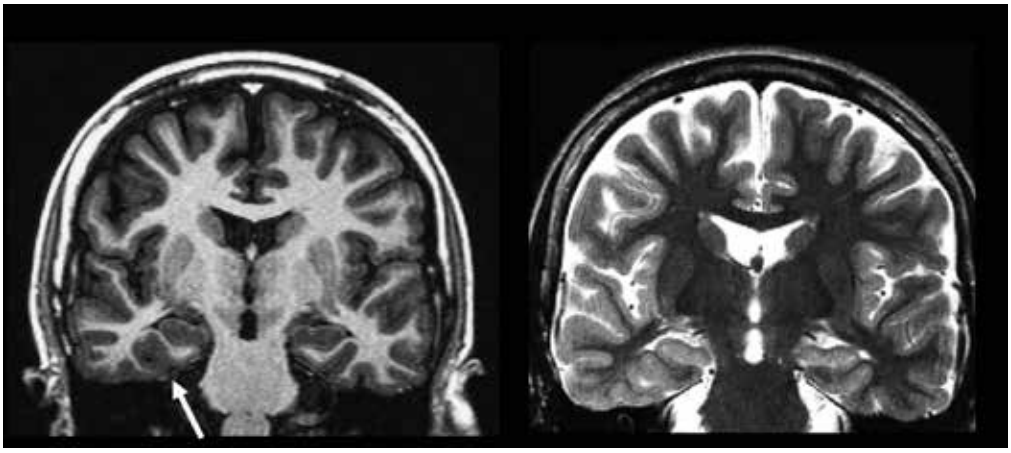

Fig. 7. Patient with MTLE and previous MRI reported as normal showing right temporal lobe lesion that was low grade ganglioglioma.

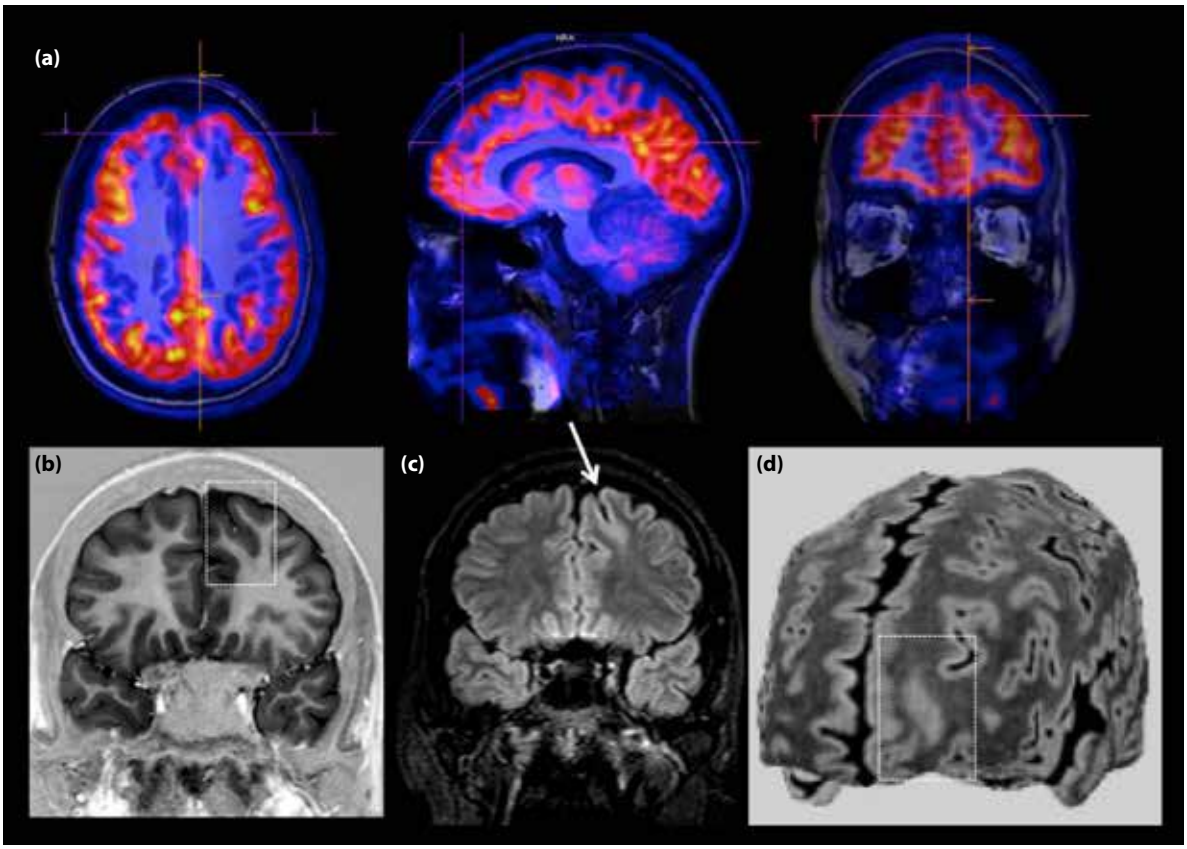

Fig. 8. Deep bottom sulcus dysplasia. **(a)** FDG-PET showing left frontal lobe hypometabolism. **(b, c)** T1WI and FLAIR MRI sequences coronal slices show cortical thickness in the left superior frontal sulcus with hyperintensity of white matter. **(d)** Curvilinear reconstruction shows similar findings and extension of these lesions, allowing surgery planning.

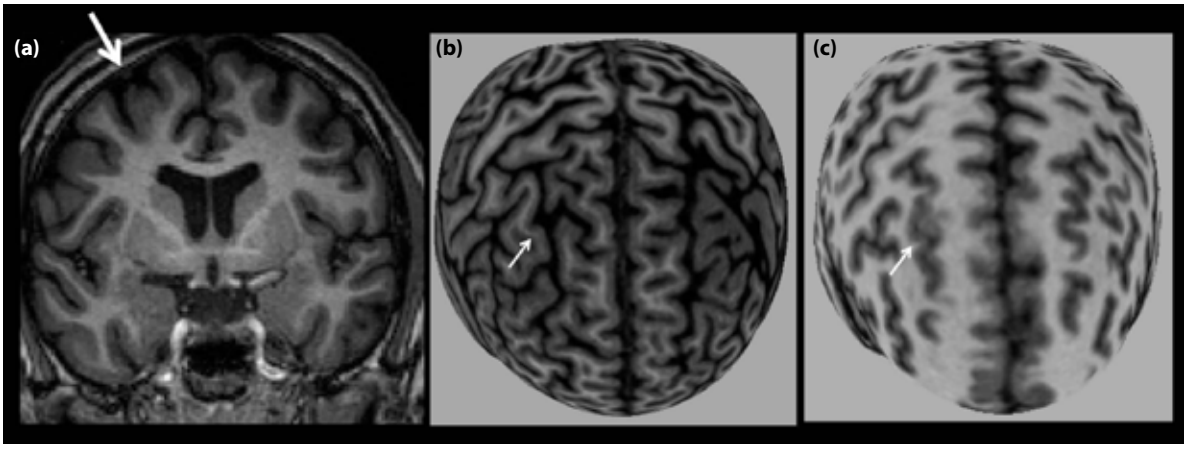

Fig. 9. T1WI coronal MRI sequence **(a)** and curvilinear reconstruction **(b)** showing changes in the pattern of brain sulci and gyri in the superior and middle frontal gyrus. Deeper curvilinear reconstruction **(c)** shows better the FCD, characterized by blurring of white and grey matter transition and cortical thickness.

Cortical Developmental Malformations

Focal Cortical Dysplasia

Focal cortical dysplasia (FCD) is an abnormality of cortical development.[33] This term designates a spectrum of histological abnormalities in the structure of the laminar cortex, with various degrees of architectural and cytopathological abnormalities,[34,35] including dysmorphic neurons and balloon cells. FCD is the most common form of developmental disorder in patients with pharmacologically intractable focal epilepsies referred to pre-surgical evaluation.[36]

The current classification subdivided FCD into three types: Type I (no dysmorphic neurons or balloon cells), Type II (dysmorphic neurons with or without balloon cells) and Type III (FCD associated with another lesion).[37]

The advent of MRI was essential for brain assessment and new MRI technology allows detection of smaller and subtler lesions. FCD is characterized on MRI by variable degrees of cortical thickening, blurring of the gray-white matter interface and hyperintense T2/FLAIR signal within the dysplastic lesion relative to normal cortex, and sometimes in the adjacent subcortical region.[38] Sometimes, changes in the pattern of brain sulci and gyri may be the main abnormalities, indicating the localization of seizure onset. Sometimes these findings can be associated with a cleft-dimple complex, defined as a cerebral spine fluid (CSF) space and a cortical dimple adjacent to a region of cortical digenesis (Figures 9, 10).[39] To validate these MRI findings, correlation with clinical and electroencephalographic data is necessary.

Another important MRI subcortical white matter abnormality is the "transmantle sign", better viewed in 3T MRI,[40,41] characterized by a line of hyperintense signal on T2WI and FLAIR and hypointense in T1WI sequences, crossing through the entire cerebral mantle, from the ventricular surface to the cerebral cortex. It is most frequently associated with FCD type II [42,43] with good seizure control after surgical treatment (Figure 11).[44]

Studies showed that about 42% of patients with MRI-negative had FCD,[45] suggesting that only routine MRI imaging may be not enough for evaluation of pharmaco-resistant epilepsy patients. Thereby, multimodal noninvasive techniques, including functional and quantitative MRI techniques are a promising option when no lesion is found.

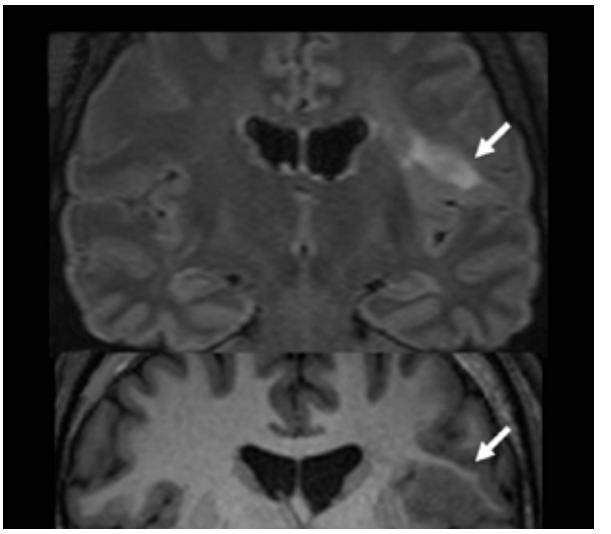

Fig. 10. T1WI axial MRI sequence showing cleft dimple-complex in the right frontal lobe.

Depending on the FCD type, MRI characteristics differ. As discussed before, MRI findings of FCD type II are usually more perceptible and clearer. The other types may show subtle findings (eg. changes in the pattern of brain sulci and gyri, deep sulci), that may indicate the location of the epileptogenic lesion together with clinical-EEG correlation.

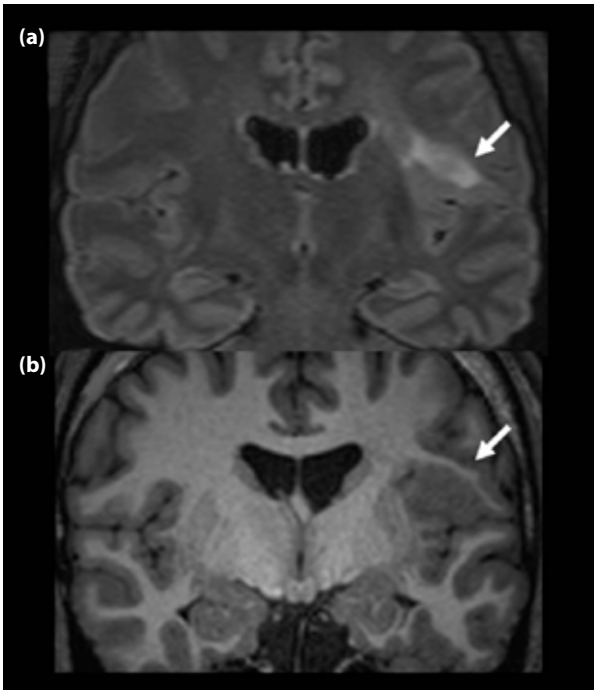

Fig. 11. FLAIR **(a)** and T1 **(b)** MRI coronal slices showing left fronto-insular FCD with transmantle sign (arrow).

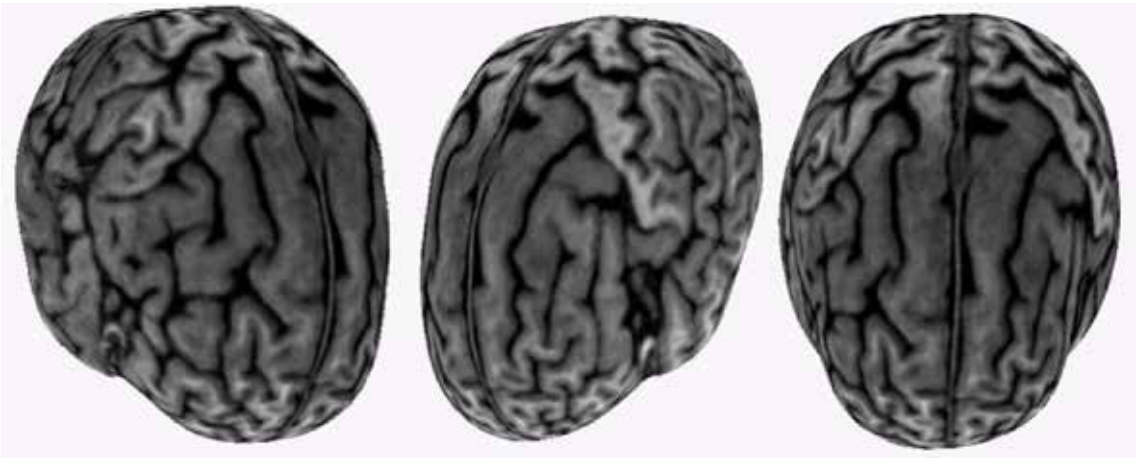

Fig. 12. Curvilinear reconstruction showing pachygiria features, characterized by simplified patterns of gyri and shallow sulci, assisting the structural imaging and providing good anatomical perspective.

Sometimes, FCD is localized at the bottom of a deep sulcus,[46,47] requiring more attention when reviewing MRI studies. Surgery is a good treatment option with excellent outcome when complete resection is achieved.[48]

Polymicrogyria

Polymicrogyria is one of the most common malformations of cortical development (MCD), characterized by excessive small and prominent convolutions separated by shallow sulci. It appears to be caused of variety mechanisms and often is associated with others malformative lesions such as cerebellar hypoplasia, callosum agenesis, periventricular nodular heterotopia, among others.[49] Polymicrogyria is not always associated with epilepsy, and in those patients with epilepsies the seizures are often well controlled with medication.

Since the advent of MRI, this type of MCD has been ever more recognized. Additional reconstruction and curvilinear

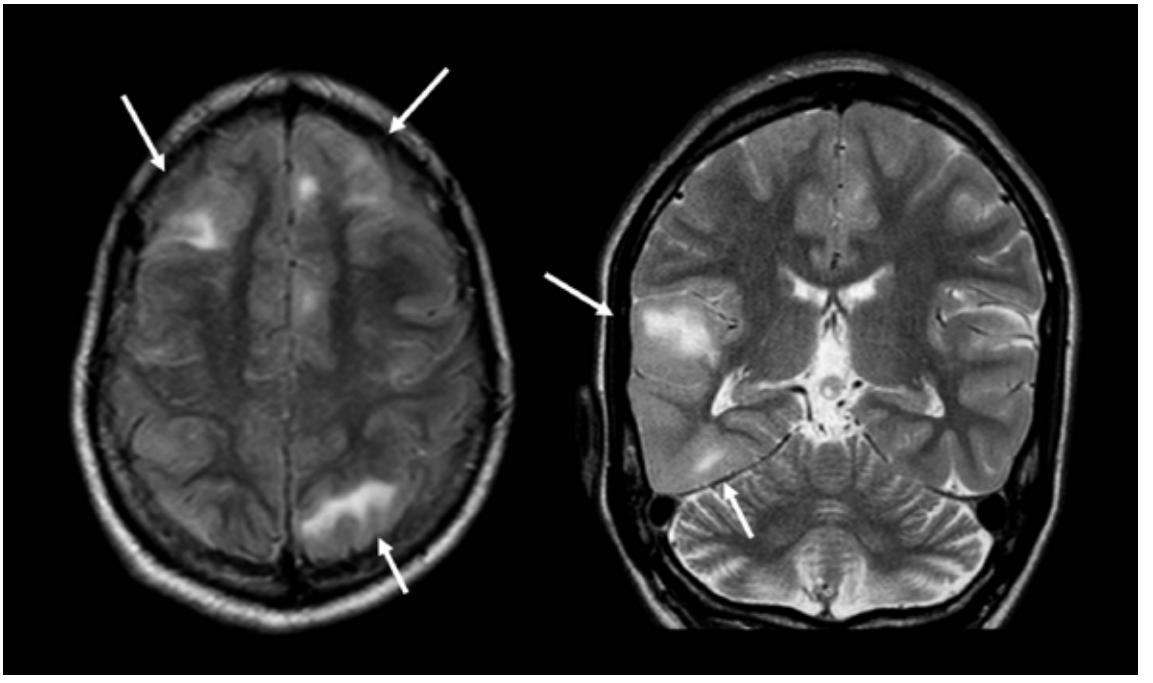

Fig. 13. FLAIR axial and coronal T2-W MRI sequences showing cortical tubers (arrows).

reformatting can better show the extent and characteristics of the lesion.[50]

Another cortical developmental malformation that is always associated with polymicrogyria is schizencephaly, which is characterized by a cleft that connects cortical surface with ventricular lumen.

Gray Matter Heterotopia (GMH)

During normal brain development, in early gestation, the neurons start their migration outward, forming the functional hexalaminar cortex. If this process is disrupted, the neurons assume an abnormal position. These ectopic neurons may stop in any area between the subependimal region and the cerebral cortex.

These malformations can be divided into four subcategories:

1. Abnormalities of the neuroependima that occurs in the begining of migration, mainly comprising periventricular nodular heterotopia (PNH);
2. Generalized abnormalities of transmantle migration such as the lissencephalies;
3. Localized abnormalities of transmantle migration including subcortical band heterotopia (SBH);
4. Abnormalities due to abnormal terminal migration comprising cobblestone malformations.[51]

Although the etiology of GMH is not yet fully elucidated, genetics may play an important role. Patients often present with pharmaco-resistant epilepsy, in addition to focal neurologic deficits.[52]

PNH is the most common GMH. It is usually located in close proximity to the ventricular wall and appears in MRI as round or oval nodules, isointense to the normal gray matter, with no contrast enhancement, projecting into the ventricular lumen or lying on the periventricular white matter.[53]

Lissencephaly has several subtypes depending on the underlying genetic abnormality. It results from the arrest of the migration process. The classic type shows smooth brain surface with agyria and cortex thickening.

In SBH (also known as double cortex) extensive plates of heterotopic gray matter are located beneath the cortex, extending from the ventricular surface outward into the white matter without continuity with cerebral cortex. Most patients are female and it rarely affects males. Other patterns of SBH have been described, including pachygyria-SBH pattern, found in males. In MRI the heterotopic bands are isointense to the cortical gray matter on all MRI sequences with variable extension and thickness.

Curvilinear reconstruction is useful to identify cortical malformations. It reveals the extension of lesions in a clearer matter (Figure 12).

Tuberous Sclerosis

Tuberous Sclerosis (TS) is a phakomatosis with dysplasias and hamartomas affecting the brain. It may be sporadic or hereditary with an autosomal dominant pattern of inheritance and often causes pharmaco-resistant seizures that start as infantile spasms in the first months of life. MRI features includes cortical tubers that may be indistinguishable from FCD type II, subependymal calcified nodules and subependymal giant cell astrocytoma (Figure 13).[54]

LEATs - Long Term Epilepsy Associated Tumors

The long-term epilepsy associated tumors (LEATs)[55] are those lesion identified in about 20 – 30% of patients who have been investigated and treated for drug resistant seizure episodes for two years or longer. These types of tumors may encompass gangliogliomas, dysembryoblastic neuroepitelial tumors, pleomorphic astrocytomas, diffuse astrocytomas, oligodendrogliomas and a few anaplastic tumors. They can occur in any part of brain, but it preferentially affects the temporal lobe region. These tumors usually present slow growth, and the main clinical feature is epilepsy.

MRI typical features are characterized by cystic alterations with or without calcification. Mural nodule can be enhanced after gadolinium injection. However, other MRI findings are associated with these tumors depending on the histological type.[56,57]

Conclusion

In the setting of clear cut abnormalities, standard MRI protocols may be sufficient. However, when standard MRI is considered normal, appropriate MRI epilepsy protocols are essential in the assessment epileptogenic lesions. Subtle MRI finding are only valued when considered together with

clinical semiology, electroencephalographic data and other imaging techniques.

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