A practical MR approach to epilepsy in infancy.

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Authors: E. Merchante Garcia, S. Navarro Herrera, P. Piñero Glez de la Peña, M. Fajardo Cascos, J. J. Sánchez Garduño; Seville/ES  
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Learning objectives

To Illustrate the clues for a successful interpretation of MRI images from pediatric patients with refractory epilepsy.

To determinate the role of MR neuroimaging in the work up of patients with intractable epilepsy.

Background

Epilepsy is a chronic neurologic disorder characterized by recurrent and spontaneous seizures.

It is a common disorder with a prevalence of 0.4% to 1% of the population. 30,000 new cases of pediatric epilepsy are reported each year and approximately 25% of them are refractory to medical therapy, representing a clinical challenge in the general population.

Role of neuroimaging

The main objective of neuroimaging in pediatric epilepsy, specially in that refractory to medical therapy, is to identify an underlying epileptogenic focus potentially amenable to surgical resection.

MRI is the modality of choice because of its excellent soft tissue contrast, high spatial resolution, multiplanar imaging capability and lack of ionizing radiation (in contrast to computed tomography).

The work up of these patients needs dedicated imaging sequences and a posterior careful review because epileptogenic substrates often present as subtle abnormalities that can be missed unless a systematic approach is used during MR interpretation.

When to perform a neuroimaging study

1. Focal onset of the seizures.
2. Focal deficit in the neurological exam.
3. Seizures refractory to first-line medical therapy.
4. Change in seizure pattern or loss of seizure control.
5. Generalized epileptic onset or non classified seizure.

MR imaging is of little benefit in those patients with idiopathic generalized epilepsy or benign epilepsy of the infancy.

Conventional neuroimaging studies are able to detect some but not all causes of pediatric epilepsy. With advances in neuroimaging previous undetectable subtle structural anomalies are now seen. The use of techniques such as diffusion tensor imaging (DTI), proton MR spectroscopic imaging (MRS), arterial spin labeling (ASL) and MRI coregistered to FDG-PET or SPECT, has recently improved the detection of the anatomic location of epileptogenic substrates and also their relationship to the eloquent regions of the brain.

MRI plays as well an important role in the postoperative period, not only identifying surgery complications but also treatment failure such as residual lesion.

**Imaging findings OR Procedure details**

Routine standard protocol in our institution includes:

Sagital 3D T1 gradient echo (slice thickness of 1 mm) with multiplanar reconstruction, coronal doble inversion recovery (DIR), coronal T1 weighted and T2 weighted, and axial FLAIR, T2, GRE T2 and diffusion weighted images.

The inability of children to cooperate (specially those younger than 6 years old) requires sedation in some cases to avoid motion artifacts.

**Epileptogenic substrates.**

They can be classified into the 7 following groups:

1. Malformations of cortical development.
2. Neoplasms.
3. Perinatal infarctions.
5. Rasmussen encephalitis.
7. Sturge- Weber Syndrome.

1. MALFORMATIONS OF CORTICAL DEVELOPMENT (MCD)

Advances in neuroimaging have increasingly recognized MCD as a major cause of seizure representing about 23-26% of all epileptogenic substrates in children and young adults with medically refractory epilepsy. Therefore, MCD must be ruled out in every epileptic pediatric patient.

MCD include a broad range of disorders resulting from the disruption of the major steps of the cortical development; depending on the step at which cortical development was first disturbed, MCD are divided into three categories:

1. **MCD secondary to abnormal neuronal and glial proliferation.**
2. **MCD secondary to abnormal neuronal migration.**
3. **MCD secondary to abnormal cortical organization.**

Any abnormality that may interfere with one of these steps including gene mutations, destructive events such as infections or ischemia or the presence of exogenous or endogenous toxins can result in a MCD.

High resolution MRI may elucidate the location, extension and type of MCD.

**HEMIMEGALENCEPHALY (HME)**

It is a severe and rare MCD that represents an hamartomatous overgrowth of all or part of a cerebral hemisphere along with an associated defect in neuronal proliferation, migration and organization.

Rarely, enlargement and dysplasia of the ipsilateral cerebellar hemisphere and brain stem are seen, a condition named as total HME.

Clinical examination is usually dominated by a severe and drug-resistant epilepsy with a progressive injury of the healthy-hemisphere.

Early surgery with hemispherectomy or hemispherotomy is the treatment of choice. The function of the resected areas are generally replaced by the other areas due to brain plasticity.
The best diagnostic clues are:

- Enlargement and cortical thickening involving all or part of the cerebral hemisphere.
- Abnormal gyral pattern with broad featureless gyri and shallow sulci.

The involved hemisphere also demonstrates white matter abnormalities reflecting altered myelination. Usually the ipsilateral ventricle is enlarged in proportion to the enlargement of the affected hemisphere with the frontal horn pointing superiorly and anteriorly. *(Fig 1).*

**CORTICAL HAMARTOMAS OF TUBEROUS SCLEROSIS (TE)**

Classically tuberous sclerosis has been characterized by the clinical triad of epilepsy, mental retardation and facial angiofibromas.

As many as 90% of patients with TE have seizures, a significant proportion of whom are refractory to medical treatment.

Central nervous system involvement in these patients is characterized by cortical tubers, subependymal nodules and subependimal giant cell astrocytoma. The ictal onset zone is often related to a tuber and the adjoining cerebral cortex.

Signal abnormalities of the cortical tubers vary depending on the degree of myelination; in neonates the tubers are seen with T1 hyperintensity and T2 hypointensity but after 6 months of age the signal intensity characteristics are reversed. They are most commonly supratentorial in location. The proportion that calcifies has not been reliable determined. *(Fig 2).*

MRI alone cannot identify the tuber responsible for epileptogenic activity. Recently, interictal MR/FDG-PET fusion imaging has shown as a promising technique in improving the location of the epileptogenic foci associated with TE.

**HETEROTOPIA**

They are collections of nerve cells in abnormal locations secondary to arrest of the radial migration of neurons.
Best diagnosis clue: nodule or ribbon isointense to gray matter located in a wrong place.

Depending on its location and morphology they can be:

- **Periventricular subependimal heterotopia:**

On imaging studies appear as as small ovoid masses that are isointense with gray matter on all imaging sequences. Most frequently are confined around trigones, temporal and occipital horns. *(Fig 3 y fig 4).*

Differential diagnosis must be done with hamartomas of TE, the latter being iso or hypointense compared to mature white matter and showing enhancement with paramagnetic contrast.

- **Focal subcortical heterotopia:**

On imaging studies appear as swirling, curvilinear gray matter mass continuous with cortex and extending to ventricle. It may appear to produce mass effect and mimic a tumor. Absence of surrounding edema and contrast enhancement, and the characteristic signal isointense to gray matter in all sequences facilitates the differential diagnosis.

Associated brain anomalies are common, more often callosal anomalies. *(Fig 5).*

- **Band heterotopia ("double cortex"):**

It is the mildest form of classic lissencephaly. On imaging it appears as a band of gray matter situated between the lateral ventricles and the cerebral cortex, which is normal in thickness and with shallow sulci. The severity of cortical anomaly is related to the thickness of band heterotopia. A more severe cortical anomaly is associated with a worse clinical prognosis of epilepsy. *(Fig 6).*

### ABNORMAL GYRAL FOLDING

- **Increased gyral foldings: Polymicrogyria:**

It is a disorder of neuronal organization. Shows a variable pattern on imaging studies depending on the degree of myelination; in unmyelinated brain the cortex looks thin while in myelinated brain looks thicker. It is isointense with the normal cortex and irregularities of the gray-white matter junction are seen. The perisylvian regions is the most common
involved area following by the frontal lobes. Anomalous venous drainage is commonly seen in these areas of dysplastic cortex. (Fig 7 y Fig 8).

- Simplified gyral folding: Lissencephaly (agyria-pachygyria complex):

Is a disorder due to abnormal neuronal migration. The term lissencephaly means smooth brain, agyria is characterized by absence of gyri and pachygyria appears on imaging as broad gyri, shallow sulci and thickened cortex. Gray-white matter junction is smooth (in contrast to polymicrogyria). (Fig 9 y Fig 10).

An important observation to distinguish pachygyria from polymicrogyria is that the sulci seen in the former are normal and in the latter are abnormal and do not correspond to those described in the classic neuroanatomy. In addition, cortex in pachygyria has a smooth inner and outer surface whereas that of polymicrogiria has an irregular interface.

**FOCAL CORTICAL DYSPLASIA (FCD)**

In contrast to other MCD mentioned above, FCD is not associated with diffuse abnormal gyration but rather with subtle focal changes that at times may only be seen microscopically.

It is now recognized as one of the most common cause of seizure in children with intractable epilepsy accounting for nearly 80% of all surgical treated cases in children under 3 years. Unfortunately these are also the most subtle lesions to identify.

Pathologic classification of FCD is made based on Palmini et al method. They can be divided into two major categories: Type I and Type II FCD; the additional finding of balloon cells subclassified the latter in type IIB FCD.

MRI findings of this entity include focal cortical thickening, blurring of the gray matter-white matter junction and gray matter T2 hiperintensity. (Fig 11). The presence of a subcortical T2 hiperintensity extending from the cortex to the ventricle often raises the suspicion of type IIB FCD.

MR/FDG PET fusion imaging can help to localized the most subtle lesions.

2. NEOPLASMS
Brain tumors in pediatric population often manifest clinically as seizures.

However, certain tumors share similar clinical and pathologic features, being referred to as epilepsy associated developmental tumors. Those included are:

- Ganglioglioma, gangliocitoma.
- Desmoplastic neuroepithelial tumors.
- Dysembrioplastic neuroepithelial tumors (DNET).
- Pleomorphic xantocytomas.

These tumors have quite similar appearance on imaging; they usually appear as cortical based lesions that are hypo or isointense on T1 weighted images and hyperintense on T2 weighted images with little or no surrounding edema. Contrast enhancement is variable.

**GANGLIOCITOMA:**

Tend to be located in the temporal lobes and may present as mixed solid and cystic masses with frequently associated calcifications. Contrast enhancement is variable. (Fig 12 y 13).

**DNET:**

It has marked variability in imaging appearance and should be suspected any time a cortical based tumor with high water component is seen in patients with long history of partial epilepsy and a normal neurologic exam or a stable long standing neurologic deficit. (Fig 14).

**DESMOPLASIC NEUROEPITHELIAL TUMOR:**

This tumor presents as a large cystic hemispheric mass containing plaque-like peripheral solid component which exhibits T2 hypointensity. (Fig 15).

Differential diagnosis must be done from cystic astrocytomas based on the T2 hyperintensity of the solid component in the latter. Other differential diagnosis includes PNET, ependimomas and pleomorphic xantocytoma.

**PLEOMORPHIC XANTOASTROCYTOMA (PXA):**
In contrast to desmoplastic tumors (tumors primarily seen in infants), PXA are usually discovered in adolescent and young adults.

Their classic appearance is that of a cystic lesion with a solid enhanced mural nodule and leptomeningeal involvement, most commonly located in the temporal lobes. Calcifications are rare.

3. MESIAL TEMPORAL SCLEROSIS

It represents one of the most common causes of epilepsy in the young adult population. The diagnosis is made based on concordance of clinical, electroencephalographic and imaging findings.

MR imaging features include atrophy of the hippocampus and increased signal intensity in the mesial temporal region on T2 and FLAIR weighted images. (Fig 16).

This patients benefits from accurate diagnosis because surgery treatment offers high cure rates.

4. RASMUSSEN ENCEPHALITIS

It is a chronic encephalitis characterized by partial motor seizure, progressive neurological symptoms and cognitive deterioration. It is also one of the most important causes of medically refractory seizures.

The most characteristic imaging feature is that of a progressive unilateral cerebral cortical atrophy. In the early disease imaging studies are typically normal; with time unilateral areas of T2 and FLAIR hyperintensity can be seen. The frontal and temporal lobe are most commonly affected.

On advanced cases may be associated to mesial temporal sclerosis.

It is essential the correlation between imaging and clinical history to make the diagnosis. Anatomic or functional hemispherectomy is the treatment of choice.
5. PERINATAL INSULTS

Focal or diffuse destructive lesions of the brain also constitute an important group of pathologic processes in children presenting with seizures.

This entity refers a cerebrovascular insult occurring around the time of birth.

Their appearances depend on brain maturity at the time of the insult and may lead to formation of porencephalic cavities, focal or diffuse encephalomalacia (fig 17) or ulegyria (fig 18) characterized by a shrunken cortex with a peculiar appearance in which the deeper portions of the gyri are more severely affected than the superficial portions.

6. VASCULAR MALFORMATIONS

Cavernomatous and arteriovenous malformations are the most common vascular malformations causing epilepsy.

The typical imaging appearance of cavernomatous malformation is a popcorn like with a heterogenous hyperintensity signal centrally surrounded by a ring of low signal intensity from hemosiderin. (Fig 19).

Arteriovenous malformations appears as a serpiginous flow blood nidus usually associated with areas of T2 prolongation in the adjoining brain.

7. STURGE- WEBER SYNDROME

Also known as encephalotrigeminal angiomatosis is an uncommon neurocutaneous syndrome marked by the association of ipsilateral facial angioma (often in the distribution of the trigeminal nerve) with an extensive pial angiomatous malformation.

The affected patients usually develop normally until they begin to suffer seizures, which progressively become refractory to medication.

MRI is considered to be the standard of reference in this syndrome. Neuroimaging studies show the most important sign, the leptomeningeal enhacement with gadolinium contrast agents in the parieto-occipital region.
Other abnormalities include avid enhancement and enlargement of the ipsilateral choroid plexus according to the extension of the leptomeningeal angioma, cerebral atrophy likely related to chronic brain ischemia, accentuated T2 shortening in the underlying white matter and cortical calcifications detected on GRE sequences. Occasionally enlarged subependimal and medullary veins may be seen. (Fig 20).

Bilateral disease can be seen in up to 20% patients.

Images for this section:

![Fig 1](image-url)

Fig 1. Left Hemimegalencephaly. (a b) Axial and coronal T1-weighted images shows enlargement of the left cerebral hemisphere as compared to the contralateral cerebral hemisphere with abnormal gyral pattern of the frontal and parietal cortices. Notice blurring of the gray-white matter junction in the affected hemisphere. (c) Axial T2 weighted image reveal straightening of the left frontal horn. (d) Axial FLAIR shows abnormal T2 hyperintensity of the white left hemisphere white matter.
Fig. 2. Tuberous sclerosis. (a y b) Axial and coronal T1 weighted images shows multiple subependimal hamartomas nearly isointense to the white matter and bilateral hypointensity cortical tubers. (c) Postcontrast axial T1 weighted images reveals enhancement of the right Monro subependimal hamartoma. Cortical tubers do not enhance. (d) sagital T2 weighted image shows the cortical tubers as hyperintense lesions.
Fig. 3. Subependimal linear heterotopia. Axial T1 (a) and T2 (b) weighted image show a layer of gray matter lining the walls of the lateral ventricles.
Fig 4. Subependimal heterotopia. (a) Axial T1 weighted image reveals multiples nodular subependimal heterotopia lining the trigones. (b) FLAIR weighted image show that the heterotopia remain isointense with gray matter.
Fig 5. Subcortical heterotopia. Axial and sagittal T1 weighted images (a & b) and axial T2 weighted image (c) shows swirling heterotopia extending from the right parietal cortex to the ventricular surface.
Fig 6. Band heterotopia. Coronal T1 IR image shows a thin layer of heterotopic gray matter deep to a normal appearance cortex.
Fig 7. Bilateral symmetrical fronto-temporal polymicrogyria. (a y b) Axial and coronal 3D GRE T1 weighted images shows thickened insular cortex associated to an abnormal sylvian fissures morphology (due to abnormal opercularization); also note bilateral abnormal frontal cortex with blurring and irregularity of the cortical-white matter junction.
Fig. 8. Bilateral fronto-parietal and perisilvian polymicrogyria in an infant. (a y b) Axial and coronal 3D GRE T1 weighted images shows abnormal fronto-temporal cortex with irregularity of the white matter-cortical interface. (c y d) Axial T2 weighted images reveals abnormal cortex extending from the frontal poles to the parietal lobes.
Fig 9. Bilateral posterior pachgyria. (a y b). Axial and sagital 3D GRE T1 weighted images shows abnormal thickened cortex, broad gyri, shallow sulci and smooth cortical-white matter junction in the parietal and occipital lobes.
Fig. 10 Diffuse pachygyria. Axial and sagittal T1 weighted images (a and b) and coronal T2 weighted images (c) shows bilateral and diffuse pachygyria more severe in the parietal and occipital lobes, with thickened cortex, broad and few gyri.
Fig. 11. Type I FCD. (a y b) Axial and coronal 3D GRE T1 weighted images shows thickened left hippocampal cortex with blurring of gray-white matter junction. (c) Coronal T2 weighted images shows abnormal T2 hyperintensity of the hippocampal gyrus.
Fig 12. Left temporal lobe ganglioglioma. (a and b) Axial T1 and T2 weighted images reveal a lobulated multicystic mass in the left hippocampal cortex without surrounding edema. (c) Axial postcontrast T1 weighted images shows that the lesion does not enhance.
Fig. 13. Left parietal lobe ganglioglioma. (a) Sagittal T1 weighted image shows a cortical based mass with mixed appearance with a predominant cystic component. (b) Postcontrast sagittal T1 weighted image reveals that the solid component enhance but the cystic component does not enhance.
Fig. 14. Left frontal dysembrioplastic neuroepithelial tumor. Axial (a), sagital (b) and coronal (c) T1 weighted images shows a heterogenous hypointense mass in the base of the left frontal lobe.
Fig. 15. Desmoplastic neuroepithelial tumor. (a) Axial T1 weighted image shows a huge left hemisphere mass with large cystic component and a small solid parasagittal component; also note the perilesional surrounding edema. (b) Axial T2 weighted image shows that the solid component exhibits low signal intensity. (c) and (d) Postcontrast axial and coronal images reveals that the peripheral solid component enhances markedly and appear to involves meningeal layers.
Fig. 16. Bilateral hippocampal sclerosis. Coronal T2 weighted image shows T2 hyperintensity and volume loss of both hippocampus.
Fig 17. Prolonged and profound neonatal hipoxic-ischemic injury with severe multicystic encephalomalacia. (a) Axial T1, (b) axial FLAIR, (c) and coronal T2 weighted images reveals white matter, cortex and basal ganglia severely damage and replaced by multiple cystic cavities of varying size separated by septae. Also note ex vacuo ventriculomegaly.
Fig 18. Ulegyria in a patients with seizures and a history of perinatal hipoxic-ischemic injury. (a b) Axial T1 and T2 weighted images shows a shrunken cortex in the parasagittal occipital regions with the deeper portions of the cortex being more severely involved than the superficial portions. Axial T2 weighted images shows abnormal hyperintensity in the occipital whitte matter.
Fig 19. Multiple cavernous malformations. (a) Axial T1 (b) coronal T2 and (c) axial FLAIR weighted images shows a right posterior frontal lobe mass with an irregular high signal intensity core surrounded by a low signal intensity rim (due to hemosiderin); also note the surrounding perilesional edema and some other small cavernous malformations in the right frontal lobe and left subependimary region (d) axial GRE reveals the paramagnetic susceptibility artifacts because of hemosiderin.
Fig 20. Sturge Weber Syndrome. (a y b) Postcontrast axial and coronal T1 weighted images shows diffuse leptomeningeal enhancement in the left hemisphere most prominent in the occipital lobe; also note the enlarged ipsilateral choroid plexus. (c) Axial T2 weighted image shows left hemisphere atrophy and enlarged of the ipsilateral subependimal vein. (d) Axial GRE weighted images shows no calcifications.
Conclusion

Medically refractory epilepsy represents a challenging clinical situation.

Neuroimaging is crucial not only for identifying epileptogenic substrates but also for determinating specific surgical treatment and predicting prognosis.

Its high spatial resolution, high soft tissue contrast, multiplanar imaging capability and lack of ionized radiation make MRI the primary technique of choice in the work up of pediatric patients with epilepsy.

Advances in neuroimaging with diffusion tensor images, arterial spin labeling, magnetoencephalography and MRI/FDG-PET fusion imaging are increasing the understanding of the underlying disease process and improving the ability to non invasive detection of epileptogenic substrates.

Personal Information


Mail to: elenamerchante@gmail.com.

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