Epilepsy in children: Review of the main causes detectable by MRI

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Learning objectives

- Describe the main congenital cerebral malformations and congenital infections that causes epilepsy in children.
- Review the different techniques and sequences in brain MRI that can improve the diagnosis.
Background

- The human cortex develops its basic structure during the first two trimesters of pregnancy as a series of overlapping steps, beginning with proliferation and differentiation of neurons, which then migrate before finally organizing themselves in the developing cortex. Abnormalities at any of these stages, be they environmental or genetic in origin, may cause disruption of neuronal circuitry and predispose to a variety of clinical consequences, the most common of which is epileptic seizures [1-3].

- Seizure disorders are very common and represent the most common cause of referrals to pediatric neurology. Seizures in children have wide variations in clinical expression with age specific presentation.

- Epilepsy, defined as recurrent unprovoked seizures, is also common with a frequency of 4-8 cases per 1000 children.

- Malformations of cortical development comprise a heterogeneous group of conditions in terms of both the timing and etiology of the developmental aberration as well as the resulting morphological phenotype, including epilepsy, developmental delay/intelectual disability and focal neurological deficits [1-3].

Clinical implications:
- Approximately 3% of newborns have major malformations.
- 60% of them remain without defined etiology.
- 20% are multifactorial (combine hereditary tendencies and nongenetic influences).
- 12-15% acquired disorders encephaloclastic.
- More than 75% of fetal deaths have brain malformation associated. Over 2,000 brain malformations have been described.

- Magnetic resonance imaging is superior in identifying congenital or developmental abnormalities and should be performed in preference to CT. MRI has revolutionized the detection of structural abnormalities in pediatric patients with epilepsy. It is important to use the proper protocol to age.
- MRI may elucidate the type, the extension and the localization of malformations of cortical development and other important disorders which can occur with epilepsy.

Some considerations on the sequences we use in MRI in children:
- **T2 FSE**: demonstration of myelin in the brain premature;
- **IRFSE**: great contrast between white x gray matter, as well as assessment of myelination
- Under 18 months is not necessary to use the FLAIR sequence.
- **Volumetric 3D T1 sequence**: Important MR sequence to facilitate the study of several cortical defects. Obtained from three-dimensional...
acquisitions, which makes it possible multiplanar reconstructions (FIG 1).

- **Diffusion weight**: Images related to differences in molecular mobility or diffusivity of water between the tissues. Cerebral infarction and hypoxic ischemic encephalopathy.

**Protocol recommended in pediatric patients with a history of epilepsy:**
- T1 volumetric (slice thickness 1 mm or less)
- Coronal FLAIR 3mm thin slices
- TSE T2 axial and coronal
- DWI
- IRFSE

- Development of the cortex can be roughly separated into three steps: cell proliferation and differentiation, cell migration and cortical organization. Any abnormality during the process of cortical formation can lead to malformations of cortical development.

- Based on pertinent aspects of central nervous system embryology, the 2005 classification of MCD classifying them according to the developmental stage during which disruption is considered to be the cause of the anomaly. There are four groups of malformations. Group I comprises disorders with decreased/increased proliferation or the proliferation of abnormal cells, and includes microcephaly, focal cortical dysplasia with balloon cells, hemimegalencephaly, tuberous sclerosis, dysembryoblastic neuroepithelial tumor and ganglioglioma/gangliocytoma. Group II includes malformations due to abnormal neuronal migration, such as lissencephaly, dystroglycanopathy and heterotopia. Group III comprises disorders due to abnormal cortical organization (including late neuronal migration), and also includes polymicrogyria, schizencephaly, cortical dysplasia without balloon cells and microdysgenesis. Finally, group IV includes all other MCD that are not otherwise classified, such as mitochondrial disorders and sublobar dysplasia [3].

- Major malformations due to abnormal neuronal and glial proliferation or apoptosis: These include hemimegalencephaly, microlissencephalies, cortical dysplasia with balloon cells (Taylor-type cortical dysplasia) and tuberous sclerosis.

- **Hemimegalencephaly** is a rare but well-known congenital malformation, consists of a group of disorders in which part or all of a cerebral hemisphere is dysplastic and enlarged [4] (FIG.2).

- **Lissencephaly**: is a neuronal migration disorder and its causes include intrauterine viral infections or viral infections in the fetus during the first trimester, ischemia early in pregnancy and genetic disorder [1-3]

- The main clinical manifestations included mental retardation, developmental delay, microcephaly, epilepsy, hearing abnormality and facial malformation.
• Lissencephaly MRI features of classical lissencephaly displayed absent or broad cerebral gyri, thickened cortex and reduced white matter, smooth border between the gray and white matter, and thin white matter (FIG 3).

• **Focal Cortical Displasy (FCD)** is now recognized to be one of the most common causes of seizures in children with intractable epilepsy, accounting for nearly 80% of all surgically treated cases in patients under three years of age [1-3].

• There are two major subdivisions of FCD. In type I, there is dyslamination of the cortical layer compared with normal cortex. In type II, along with cortical dyslamination, there are also dysmorphic neurons. Type IIB corresponds with FTD (focal transmantle dysplasia), as described by Taylor, and is characterized by dyslamination, dysmorphic neurons and the presence of balloon cells. Characteristic MRI findings of FCD include focal cortical thickening, blurring of the gray-white matter junction, and gray-matter T2 hyperintensity. Nuclear Medicine (PET), can be used as co-adjuvants in the diagnosis of these lesions, demonstrating increased brain activity in the affected areas. (FIG 4).

• **Tuberous sclerosis** is a rare autosomal-dominant neurocutaneous syndrome affecting about 1 in 6000 live births and is characterized by the presence of benign congenital tumors in multiple organs, and including cerebral, cardiovascular, pulmonary, renal, retroperitoneal, hepatic, gastrointestinal and skeletal involvement. Common cerebral involvement are cortical tubers, subependymal nodules, subependymal giant-cell astrocytomas and whitematter abnormalities. Other rare cerebral disorders include: mild dilatation of lateral ventricles, cerebellar atrophy, dysgenesis of the corpus callosum, Chiari malformation, microcephaly, macroencephaly and arachnoid cysts [1,3].

• **Cytomegalovirus** has been suggested to have a teratogenous influence during the migration of neural cells from the ventricular zones to the cortex during the gestational period. Congenital cytomegalovirus infection can lead to severe neurological sequelae. Microcephaly, cerebral palsy and epilepsy are common clinical findings. The spectrum of brain MR abnormalities in symptomatic congenital CMV infection is extremely wide and included: cortical malformations, ventriculomegaly and hippocampal dysplasia Radiological findings show connection between onset of infection and brain imaging, from lissencephaly, pachgyria, polymicrogyria, schizencephaly, calcification, cerebellar hypoplasia and/or hypoplasia/agenesis of corpus callosum as a result of an early infection, to white matter abnormalities including disturbed myelination as a result of a late infection[4,5].
Fig. 1: Volumetric 3D T1 sequence

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Fig. 2: Hemimegalencephaly. Coronal T2-weighted: Enlargement of the right cerebral hemisphere with moderate asymmetric hydrocephalus.

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Fig. 3: LISSENCEPHALY

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Fig. 4: Cortical dysplasia in the left parietal lobe with PET demonstrating metabolic hyperactivity in correspondence.

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Findings and procedure details

- The MRI scans performed at the HCN (Clinical Hospital of Niterói), Rio de Janeiro, Brazil, in children with epilepsy were reviewed.
- We did a review of all children who underwent brain MRI with clinical indication of epilepsy in the period 2006-2013. 35 patients were selected. We had 19 males and 16 females ranging in age from 5 months to 18 years (FIG 5).

- All examinations were performed on equipment 1.5 tesla MRI under anesthetic sedation, with the patient properly monitored throughout the period of examination. Their consent by the patient's parents was signed authorizing the procedure. Of the 35 cases 18 had normal MRI and 17 had changes (FIG 6).

- We had four cases of sequelae of hypoxic-ischemic lesions, three cases of cortical dysplasia, two cases of posterior fossa cyst and one with Dandy-Walker. We also had a patient with an arachnoid cyst in the left temporal region.
- Two patients had delayed myelination with dysgenesis of the corpus callosum.
- Two patients had Tuberous sclerosis.
- One patient had rotational abnormality of the hippocampus and other a cavernoma in the high right parietal region.

- The patient with Dandy-Walker still presented in association: agenesis of the corpus callosum and cortical dysplasia with polymicrogyria and heterotopia of subependymal gray substance (FIG 7,8).

- DANDY-WALKER - 3 criteria:
  - Enlargement of the posterior fossa with superior displacement of the tentorium (torcular-lambdoid inversion)
  - Severe hypoplasia or agenesis of the cerebellar vermis
  - Cystic dilatation of the 4th. ventricle: without communication with the subarachnoid space

- Dandy-Walker variant:
  - Features similar malformation, but not fulfilling the three criteria
  - Cerebellar vermis hypoplasia and cyst without expanding posterior fossa
  - Incomplete agenesis of the vermis
  - Cases where the cyst communicates with the subarachnoid space.
Posterior fossa cysts are usually identified prenat(129,121),(878,851)

Polymicrogyria is a malformation of cortical organization, and is one of the most common MCD, and describes the process of normal cerebral cortical development disturbed late during the stage of neuronal migration or early in the stage of cortical organization. Causes include prenatal infections (cytomegalovirus), prenatal ischaemia or exposure to toxins, chromosomal abnormalities and inborn errors of metabolism [7].

Among the four cases of sequelae of hypoxic-ischemic injury, we had one where there was involvement of the frontal lobes with hemorrhagic foci. In this case, the use of T2-weighted sequences in the coronal plane and were useful in the evaluation of the lesions. (FIG 9,10).

Epilepsy is frequent in children with delayed presentation of perinatal stroke and is associated with initial presentation with seizures and infantile spasms at any point in time. Cognitive disability often accompanies epilepsy in these children[8-9].

One of our patients with cortical dysplasia of Taylor, had an area of encephalomalacia associated. In this case, the use of volumetric T1 sequences with later reconstructions collaborated in view of these changes (FIG 11,12).

We had a case of arachnoid cyst in the left temporal fossa, which had refractory epilepsies control (FIG 12).

In cases of tuberous sclerosis, subcortical hamartomas were seen. Small giant cell astrocytomas were also found in two cases in this series (FIG 13).
Fig. 5: Children with epilepsy.

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**Fig. 6:** 35 children with epilepsy: MRI scans of normal and abnormal findings.

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**Fig. 7:** Female. 3 years: Dandy Walker. Agenesis of corpus callosum.

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**Fig. 8:** Same patient as previous figure, showing up multiple small gyri. Polymicrogyria.

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**Fig. 9:** Axial sequences: FLAIR-weighted gradient-echo and IRFSE demonstrating frontal cortico-subcortical areas, bilaterally, with hemorrhagic foci.

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**Fig. 10:** T2-weighted coronal planes: Same patient in the previous figure, showing a reduction of the thickness of the orbital gyri of the frontal lobes.

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**Fig. 11:** FLAIR, diffusion and ADC map: Thickening of the parietal and occipital cortex of the left with loss of differentiation of white matter and gray wolves. Area of encephalomalacia parietal left with perilesional gliosis, causing retraction of the ventricular atrium.

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**Fig. 12:** Curvilinear volumetric reconstruction showing the area of the left parietal cortical dysplasia.

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**Fig. 13:** Arachnoid cyst in the left temporal region. Axial T2-weighted and IR axial planes and T2-weighted in coronal plane.

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**Fig. 14:** Tuberous sclerosis with subependymal nodules left (giant cell astrocytoma) and left frontal subcortical hamartoma.

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Conclusion

• The recognition and correct diagnosis of the causes of epilepsy are important to provide the patient an improvement in their treatment.

• MRI imaging, due to its excellent contrast differentiation and multiplanar capabilities as well as the development of even newer techniques, provides important information for the diagnosis and monitoring of these patients.
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