MALFORMATIONS OF CORTICAL DEVELOPMENT: A PICTORIAL REVIEW

Padmaja K. Naidu, M.D.
Usha D. Nagaraj, M.D.
William T. O’Brien, Sr., D.O.

AOCR Annual Conference 2018
Scottsdale, Arizona
Learning Objectives

• Review the major phases of cerebral cortical development & normal cortical structure

• Identify the distinguishing characteristics of each of the major malformations of cortical development (MCDs) on MRI

• Identify the phase of cerebral cortical development in which an abnormality occurred for a given MCD

• Understand the role of imaging and importance of an interdisciplinary approach in the care of patients with refractory epilepsy due to MCDs

The authors have no disclosures
Outline

• Cerebral Cortical Development
• MCDs with Imaging Examples
  – Organized by phase in which the MCD occurs
• Optimizing Imaging in MCDs
• Importance of an interdisciplinary approach
• Summary
Development of the Cerebral Cortex
This intricate, complex process can be divided into 3 general phases (below) that overlap in time

**PROLIFERATION/ APOPTOSIS**
- Begins in germinal zones during 4-5th week of gestation
- Germinal zone: along lateral ventricle margin
- Both neurogenesis and gliogenesis

**MIGRATION**
- Greatest between 8 - 24 weeks of gestation, ends by 27 weeks
- Neurons migrate along fascicles formed by radial glial cell processes, from germinal zones peripherally to cortex
- "Inside-out" pattern (early migrating cells are located deeper in cortex)

**ORGANIZATION/ MATURATION**
- 28-40 weeks
- Cortex is organized into 6 functional layers
- Establish connectivity with other neurons
- Neuron location determined by genetics and interactions with other CNS components
Cerebral Cortex

- **Normal neocortex**
  - 6-layered neocortex present in over 90% brain
    - Olfactory paleocortex & hippocampal archicortex composed of 3 layers

- **Normal neocortex is 1-3 mm in thickness**
  - Thinner at depth of sulcus (*
  - Thicker at crown of gyrus (green arrow)

Magnified T1-weighted image demonstrating normal gyri. (* indicates depth of sulcus, green arrow indicates crown of gyrus.)
Malformations of Cortical Development (MCD)

MCDs are micro- or macroscopic abnormalities of the cerebral cortex that result from interruption of normal cortical formation.

| This presentation will review the imaging findings of the following MCDs: |
| --- | --- |
| - Microcephaly with Simplified Gyral Pattern (MSG) |
| - Classic Lissencephaly (agyria-pachygyria) |
| - Band Heterotopia |
| - Gray Matter (GM) Heterotopia |
| - Polymicrogyria (PMG) |
| - Schizencephaly |
| - Focal Cortical Dysplasia |

<table>
<thead>
<tr>
<th>Most patients with MCDs have epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>- MCDs cause 25-40% of intractable, medically refractory epilepsy</td>
</tr>
<tr>
<td>- Exceptions: MSG</td>
</tr>
</tbody>
</table>
Malformations of Cortical Development (MCDs)

• MCDs have been increasingly recognized in recent decades due to improved MRI resolution

• At least 75% of patients with MCDs have epilepsy

• The presence of an MCD in and of itself is associated with medically refractory epilepsy
  
  – Surgery is becoming more commonplace in the setting of refractory pediatric epilepsy
Phases of Cortical Development in Which Specific MCDs Occur (Some Involve More Than One)

PROLIFERATION/ APOPTOSIS

- Microcephaly with Simplified Gyral Pattern
- Type IIb Focal Cortical Dysplasia
- Hemimegalencephaly

MIGRATION

- Lissencephaly
- Band Heterotopia
- Gray Matter (Nodular) Heterotopia

ORGANIZATION/ MATURATION

- Schizencephaly
- Polymicrogyria
- Focal Cortical Dysplasia Types I and IIa
Disorders of Proliferation

Microcephaly with Simplified Gyral Pattern (MSG)

- Results from ↓ proliferation or ↑ apoptosis of neurons/neuronal precursors
- MRI shows simplified gyral pattern with shallow sulci
- Microcephaly with head circumference (HC) > 3 standard deviations below mean
  - Decreased craniofacial ratio
7-year-old with retinal dystrophy, microcephaly, and developmental delay. Sagittal T1-weighted image (A) demonstrates small size of the cranium relative to facial structures. The corpus callosum is foreshortened but fully formed (*). Axial T1 (B) & T2-weighted images (C) show relative simplification of the gyral pattern, particularly in the frontal lobes; sulci are half of their normal depth or less (→). The brain is otherwise normal in morphology & signal with a preserved gray-white junction (→) and appropriate cortical thickness. Findings are compatible with primary MSG.
Focal Cortical Dysplasia (FCD) is defined as cortical disorganization with abnormal laminar architecture
  – can be associated with heterotopia & polymicrogyria

FCDs are categorized according to 2011 ILAE classification (see following slide)

FCDs are the most important etiology of focal, medically refractory epilepsy
  – found in almost ½ of pathologic specimens from surgery done for refractory epilepsy

Type IIb FCD is considered a disorder of proliferation

The remainder of FCDs are considered disorders of late migration and organization and will be presented accordingly
Abbreviated ILAE Classification

- **FCD Type I** – Architectural cortical abnormalities (such as abnormal lamination)

- **FCD Type II** – Architectural abnormality and cell abnormality consisting of dysmorphic neurons or balloon cells
  - Balloon cells also seen in tubers of tuberous sclerosis upon pathologic examination
Disorders of Proliferation

Focal Cortical Dysplasia, Type IIb

- Imaging findings of FCDs include:
  - Thickened cortex
  - Blurring of gray-white (GW) matter jxn
    - ↑ cortical and/or WM signal
  - Transmantle signal abnormality that extends to and tapers towards ventricular margin; usually in Type IIb
  - “Bottom of sulcus” configuration – GW blurring at the depth of a sulcus that extends in a transmantle fashion (also associated with Type IIb)
  - Abnormal gyral pattern
  - ↓ focal or lobar volume

9-year-old with drug-resistant epilepsy. Axial T2-weighted image shows a large wedge-shaped area of T2-hyperintensity involving both GM & WM in the right parietal lobe. Margins of the abnormality are indicated by (→).

Note additional findings of scattered cortical thickening, GW junction blurring (→), as well as ill-defined extension and tapering into the WM along the anterior margin of the lesion (*) on this image.
Disorders of Proliferation
Focal Cortical Dysplasia, Type IIb

- Note transmantle extent of the wedge-shaped T2/FLAIR hyperintense lesion on high resolution FLAIR images in the same patient

- Surgical resection: Type IIb FCD

- Patient has been seizure free since surgery (> 1 year)

Sagittal high resolution FLAIR image in the same patient shows the wedge shaped area of right parietal hyperintensity extending from the cortex (delineated by [→]) to the ventricular margin (→).
Disorder (primarily) of Neuronal Proliferation

**Hemimegalencephaly**

- Hemimegalencephaly results from hamartomatous overgrowth of whole or part of hemisphere.
- Origin uncertain – abnormality of cell growth/lineage with secondary migratory component versus over-proliferation with decreased apoptosis.
- Also described as a hemispheric version of FCD Type II.

8-year-old with intractable epilepsy. Note left holohemispheric overgrowth (→), architectural distortion, and thick cortex (*) with blurred GW interface (→) on this coronal T1-weighted image.
Hemimegalencephaly

- This T2 image shows typical findings of HME, including:
  - Cerebral hemispheric overgrowth
  - Abnormal gyration and thick, distorted cortex (→)
  - Blurred GW junction (→)
  - Hypertrophied, T2 hyperintense WM signal abnormality (more focal in the left paramedian parietal WM) (*)
  - Lateral ventricle *enlargement* (*)
  - Displacement of the left occipital lobe & posterior falx to the right of midline (*)
Hemimegalencephaly

- Typically, patients have early onset of intractable epilepsy
- Poor prognosis, both functionally & in general
- Treated with anatomic or functional hemispherectomy

Coronal and axial T2 weighted images of the brain from fetal MRI. Both images show asymmetric enlargement of one of the cerebral hemispheres, indicating hemimegalencephaly. Lower signal of WM in the affected hemisphere (*) may represent inherent architectural abnormality or relate to seizure activity.
Disorders of Migration

Lissencephaly

- **Type I (Classic):** Arrested neuronal migration
  - MRI shows
    - Complete or partial lack of gyration
      - Gyri are wide, shallow & featureless (pachygyria – agyria spectrum)
        - Some temporal gyration is visible here
    - Thick cortex (12-20 mm)
      - Cell arrest in radial columns
      - 4 layer (superficial to deep)
        - **Molecular layer** (not visible)
        - Thin outer cortical layer
        - Thin T2-hyperintense cell-sparse zone
        - Thick inner cellular layer of GM

Coronal T2-weighted image with near complete agyria in a 6-month-old with classic lissencephaly. Arrows denote the three visible layers, including the thin outer cortical layer, thin T2- hyperintense cell sparse zone and thick inner cellular layer of GM that reflects neuronal arrest. Wide, underoperculized Sylvian fissures are indicated by the (•).
Disorders of Migration

Lissencephaly

- Multiple causative mutations result in heterogeneity of phenotypes
  - Most cases are due to a specific genetic defect
  - Can be partial, with differences in area affected depending on gene product
    - LIS1: posterior hemisphere predominance
    - DCX1: anterior predominance
  - On a spectrum with band heterotopia

Axial T1 (left) and T2 (right) weighted images from the same patient demonstrate featureless, thick cortex, a decrease in supratentorial WM (& WM arborization), and shallow, underdeveloped Sylvian fissures (→) that result in a “figure 8” appearance of the brain. Mild lateral ventriculomegaly is present.
Disorders of Migration

Lissencephaly

- Fetal MRI is useful for early detection of MCDs

- When interpreting MRIs of the fetus or premature neonates, consider patient’s gestational age prior to using the term “lissencephalic”
  - Smooth appearance of the brain is normal until at least 20 weeks gestation
  - Parieto-occipital and calcarine fissures should be visible @ 24 weeks
    - If absent & have shallow sylvian fissures, suspect lissencephaly

Coronal & axial T2-weighted images of a 31 week, 3 day GA fetus with lissencephaly demonstrate agyria and exceedingly shallow Sylvian fissures in utero. Normally, at 31 weeks gestation, the Sylvian fissures are deeper and demonstrate more complex branching that delineates insular contours; numerous additional major sulci should also be evident. Yellow arrow indicates thick inner cellular layer; tip of green arrow indicates the cell sparse zone.
Disorders of Migration

Band Heterotopia due to DCX-1 Mutation

• Band heterotopia refers to arrested migration of a group of neurons
  → results in a thick symmetric band (AKA laminar band) of GM heterotopia
  – Located anywhere in WM from germinal zone to subcortical region
  – This patient had a DCX mutation
    • X chromosome (Xq22, Xq23)

8-year-old with intractable epilepsy
Axial T1-weighted image shows thick band heterotopia (→).
Disorders of Migration

**Band Heterotopia due to DCX-1 Mutation**

- Band heterotopia is on a spectrum with classic lissencephaly
  - considered to be a mild form thereof

- MR findings:
  - See band of heterotopic GM as isointense to cortex on all sequences
  - Cortex may be secondarily thinned

8-year-old with intractable epilepsy. Coronal T2-weighted image shows thick band heterotopia (→).
Disorders of Migration

Nodular GM Heterotopia

- Nodular heterotopia refers to ectopic areas of neurons due to arrested/disrupted migration
  - Occurs along course of migration
    - Located anywhere from subependymal region to subcortical WM

- Focal or diffuse

- MRI shows:
  - Nodular areas isointense to cortex on all sequences

A couple small nodules of T2 hypointense signal (similar to cortex, →) are seen along the posterior margins of the lateral ventricles on T2-weighted images from a fetal MRI at 23 weeks GA for a Chiari II malformation (not shown). These areas were suspicious for nodules of subependymal GM heterotopia.
Disorders of Migration

Nodular GM Heterotopia

• Axial T2-weighted images from the same patient after delivery confirm the diagnosis of subependymal nodular heterotopia (→)

• 80-90% GM heterotopia patients have intractable partial epilepsy
Axial T2-weighted images in a 3-month old patient with Aicardi syndrome (infantile spasms, dysmorphic/absent corpus callosum, and ocular abnormalities) show small foci of GM heterotopia (→) in the right frontal WM and along the subependymal right lateral ventricle. Note the different points of neuronal arrest along the path of migration reflected by these 2 separate areas.

Asymmetric architecture is noted on a wider scale in the right frontal lobe (light blue oval).

An interhemispheric cyst is seen on the left posteriorly, displacing adjacent cortex (*).
Disorders of Late Migration & Organization: 

**Schizencephaly**

- **Schizencephaly** refers to a transmantle cleft through brain parenchyma
  - Type I: Closed lip
    - Walls of cleft apposed
  - Type II: Open lip
    - Walls of cleft separated by CSF

- **Lined by dysplastic GM**
  - PMG
  - GM heterotopia
  - Isointense to cortex

- **Due to a premigrational insult to the germinal matrix**

Fetal MRI. Axial SSFP T2-weighted images in a 28 week GA fetus. A GM lined parenchymal cleft extends from the cortical surface of the frontal lobe to the lateral ventricle margin (→), indicating a Type II (open-lip) schizencephaly. Note subtle dimple along the ventricle margin (inferior-most image) The septum pellucidum is absent.
Disorders of Late Migration & Organization: Schizencephaly

- Bilateral & open lip forms have worse prognosis
- May see “dimple” along lateral ventricle wall with CSF extending into GM lined cleft
- Associated with septo-optic dysplasia (SOD)
  - Absence of septum pellucidum
  - Optic nerve hypoplasia
  - Pituitary dysfunction
  - +/- Migrational abnormalities

Postnatal imaging confirms the presence of schizencephaly in the left frontal lobe (→). Note thick, T2 hypointense dysplastic cortex lining the cleft. Subtly greater T2-hypointensity of cortex in this region (*) may reflect a further component of migrational abnormality or relate to seizure activity.

The septum pellucidum (SP) is absent; the optic nerves were normal (not shown). The patient did not have SOD despite a suspicion for it on fetal imaging.
Disorders of Late Migration & Organization:

**Focal Cortical Dysplasia, Type I**

• This nonenhancing ill-defined, expansile T2-hyperintense lesion within the left mesial temporal lobe cortex & subcortical WM was worrisome for tumor over FCD
  – FCD vs. low-grade tumor is a common DDx in the setting of pediatric seizures

• Patient underwent partial left temporal lobectomy
  – Pathology: FCD type Ib with gliosis
  – No tumor

• Patient has been seizure free since surgery (> 1 year)

11-year-old with intractable partial complex seizures. Coronal T2-weighted image (top) and coronal post-contrast T1-weighted images (bottom) show a nonenhancing bulky area of T2-hyperintensity (→).
Disorders of Late Migration & Organization: Focal Cortical Dysplasia, Type IIa

- This area of left parietal T2-hyperintensity and dysmorphic gyri was nonenhancing & stable for > 2 years
  - Involves both GM & WM
- Surgical resection: Type IIa focal cortical dysplasia
- Patient has been seizure free since surgery (> 1 year)

9-year-old with intractable epilepsy. Axial T2-weighted image shows wedge-shaped left parietal T2 hyperintensity with gyral dysmorphism (→).
Disorders of Late Migration & Organization: 

**Polymicrogyria**

- With polymicrogyria, neurons reach cortex, but organize abnormally
- May be genetic or result from intrauterine insult (e.g. infxn/ischemia)
- Imaging shows multiple small undulating gyri
- Cortex may appear normal or often thickened

17-year-old with migraine headaches. Note small undulating gyri with thickened cortex within the left frontal operculum and insula (→), compatible with polymicrogyria.
Disorders of Late Migration & Organization: Poly microgyria

- **Perisylvian location is most common**
  - Can be bilateral (perisylvian syndrome)

- **MRI findings:**
  - Irregular cortical surface with *microserrated contour*; may be depicted well on parasagittal images
  - Thick cortex (5-7 mm)

Sagittal T1-weighted image demonstrates abnormally thick cortex with an undulating contour along the Sylvian fissure due to polymicrogyria.
Disorders of Late Migration & Organization: 

**Polymicrogyria**

Axial and coronal T2-weighted images of the brain in an 8-year-old with medically refractory epilepsy show asymmetric cortical architecture between the cerebral hemispheres. Areas of *undulating microserrated gyri with thickened cortex* within the right hemisphere (→) include the perisylvian region and are compatible with *polymicrogyria*. A flat and broad gyrus within the lateral right frontal lobe is an example of *pachygyria*. 
Imaging in MCDs

- Multiplanar, multisequence MRI done on higher strength (3T) scanners is preferable
  - Need high spatial resolution and contrast
    - Multichannel head coils are better than conventional
    - Conventional sequences + a volumetric acquisition
      - Volumetric multiplanar T1 ideal for cortical architecture
    - T2 FLAIR is sensitive to structural abnormalities, especially FCDs
Imaging in MCDs

• Exam and interpretation should be tailored to patient’s clinical scenario as much as possible
  – If available, review EEG results for type of seizure activity & potential site of activation or localization

• Additional studies, such as PET and SPECT, aid in the detection of subtle MCDs
Axial PET image shows focal hypometabolism in the right anterior frontal lobe (→). This triggered reevaluation of the patient’s prior MRI (12-year-old with intractable epilepsy). Upon additional review, a funnel shaped area of high FLAIR signal was found in the same region (→), compatible with a subtle cortical dysplasia (“bottom of the sulcus sign”). The transmantle extent is best seen on sagittal FLAIR images (→).
Interdisciplinary Approach to MCDs

• An interdisciplinary epilepsy conference occurs at most centers that surgically treat epilepsy

• This opens up a dialogue between the different subspecialists involved
  – Triggers additional review of imaging studies, potentially increasing the diagnostic yield of each study for subtle lesions

• Provides radiologists with ongoing education concerning new and evolving concepts and techniques in the field

• Ultimately, it allows each radiologist to understand how best they can aid their epileptologists to improve patient outcomes
  – Tailoring exams, integrating new and advanced imaging techniques
  – Increasing awareness of subtle findings
Summary

• MCDs are a heterogeneous group of disorders involving abnormal formation of the cerebral cortex

• Knowledge of when the insult that results in a particular MCD occurred in the context of cerebral cortical development helps explain the appearance on MRI

• An interdisciplinary approach is critical to the work-up and management of medically refractory epilepsy in children
References & Suggested Readings


Thank you!