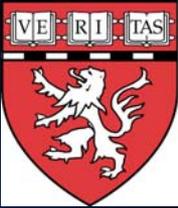


*Neuroimaging of Seizures:
Malformations of Cortical
Development*

Miya Bernson, HMSIII and Gillian Lieberman, MD
Department of Radiology
Beth Israel Deaconess Medical Center

If radiology is the study of *living anatomy*,

then radiology of congenital anomalies
is the study of *living embryology*...

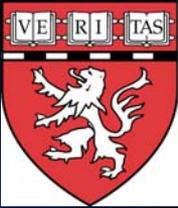


Definition

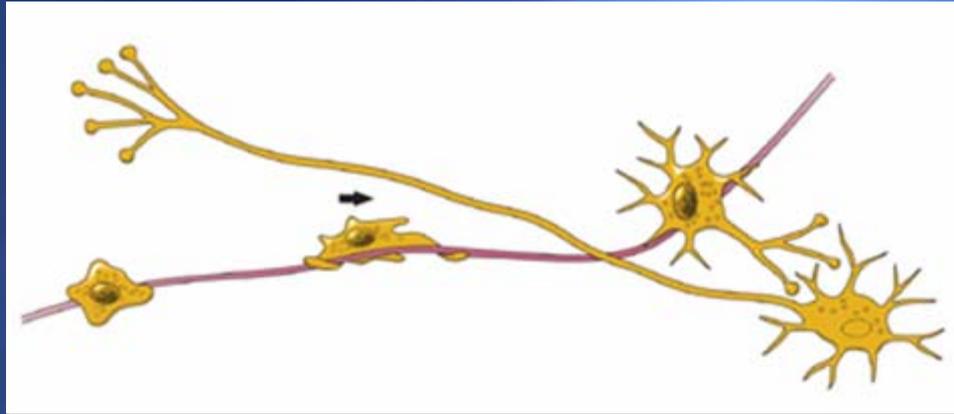
Malformations of cortical development --
disruptions in the normal development of the
cerebral cortex, including disordered:

- ⊕ Neuronal proliferation
- ⊕ Neuronal migration
- ⊕ Cortical organization

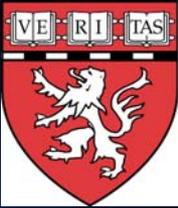
resulting in focal or global abnormalities of
structure and function.



Cortical Embryology: From Stem Cells to the First Layer



1. Primitive cells **originate** at the neuroepithelium of the neural tube
2. These cells **proliferate** and become neuroblasts
3. Most neuroblasts **migrate** radially along glial scaffolding to the marginal layer



Cortical Embryology: Architectural Organization

4. Outer layers of cortex form later
5. The cortex **organizes** and folds to form the sulci and gyri
6. The neurons undergo **differentiation**, synaptogenesis, and axonal pathfinding
7. Cerebral **myelination** begins around 40 weeks gestation and is completed by age 2

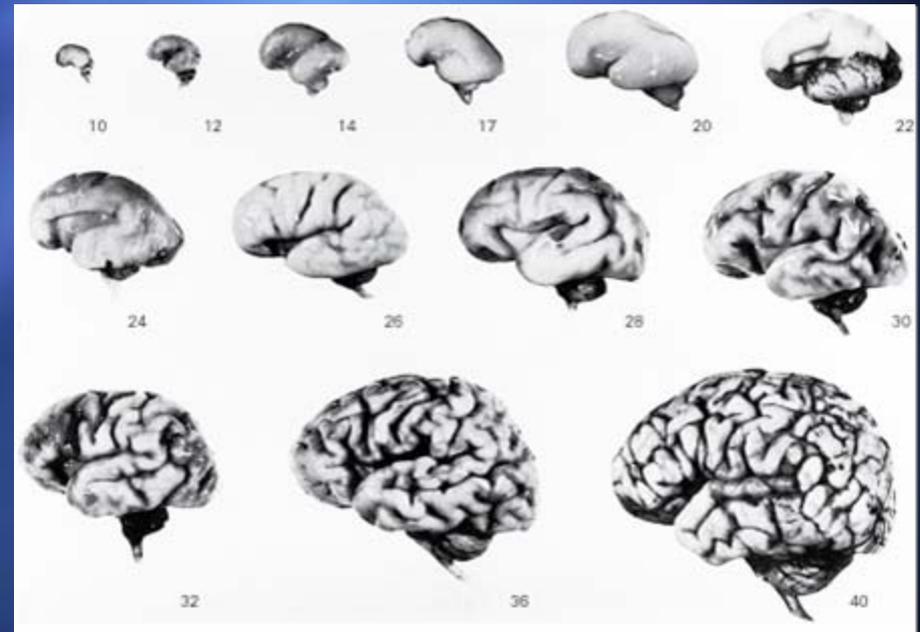
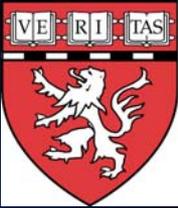


Image from Ropper AH, Samuels
MA: Adams & Victor's Principles
of Neurology, 9th Ed.

Cortical development proceeds in a series of precisely ordered steps. What happens when one of these steps is perturbed?



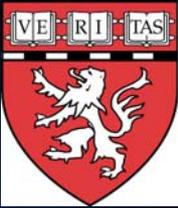
Disruptions in Cortical Development

⊕ **Neuronal proliferation**

- ⊕ Microcephaly/macrocephaly
- ⊕ Cortical dysplasia with balloon cells
- ⊕ Tuberous sclerosis (cortical hamartomas)
- ⊕ Dysembroblastic neuroepithelial tumor and other neoplasias

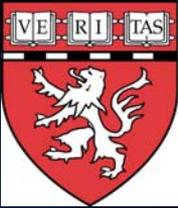
⊕ Neuronal migration

⊕ Cortical organization



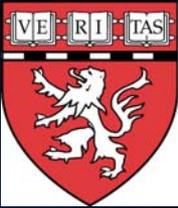
Disruptions in Cortical Development

- ⊕ Neuronal proliferation
- ⊕ **Neuronal migration**
 - ⊕ Lissencephaly/subcortical band heterotopia spectrum
 - ⊕ Subependymal heterotopia
 - ⊕ Subcortical heterotopia
- ⊕ Cortical organization



Disruptions in Cortical Development

- ⊕ Neuronal proliferation
- ⊕ Neuronal migration
- ⊕ **Cortical organization**
 - ⊕ Polymicrogyria/schizencephaly
 - ⊕ Cortical dysplasia without balloon cells

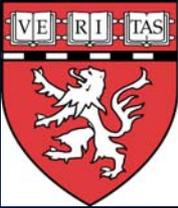


Significance of Detection

Malformations of cortical development are inherently epileptogenic.

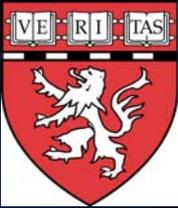
Their detection and characterization can:

- ⊕ Explain previously idiopathic/cryptogenic epilepsy
 - ⊕ Approximately one-half of epilepsy patients have some form of cortical dysplasia (and 1.7% of normal brains at autopsy)



Significance of Detection

- ⊕ Support a diagnosis of focal epileptogenesis
 - ⊕ Implications for choice of antiepileptic agent
 - ⊕ Implications for possibility of surgical resection, particularly for pharmaco-refractory epilepsy
 - ⊕ Significant chance (60% in a combined series) of becoming seizure-free
- ⊕ Aid in surgical planning
 - ⊕ Extent of resection is the most important determinant of post-operative seizure control
- ⊕ In the future: identify and treat patients at risk before they ever seize?

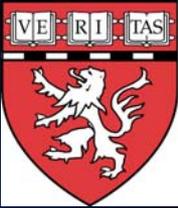


Menu of Tests

Computed tomography (CT) is excellent for cerebrovascular and bony pathology.

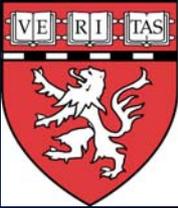
However, **magnetic resonance imaging (MRI)** is preferred over CT for imaging of neurological diseases, due to:

- ⊕ Better soft tissue contrast resolution
- ⊕ Multiplanar views
- ⊕ Multiple sequences and use of contrast
- ⊕ No streak artifacts from dense bone or metallic objects
- ⊕ No ionizing radiation



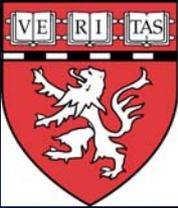
Practice Parameters: Adults

- ⊕ For adults with first unprovoked seizure:
 - ⊕ EEG
 - ⊕ MRI (or CT)
 - ⊕ Metabolic and other lab tests as appropriate



Practice Parameters: Children

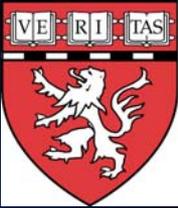
- ⊕ For children with first unprovoked (nonfebrile) seizure:
 - ⊕ EEG
 - ⊕ Consider neuroimaging based upon individual characteristics:
 - ⊕ EEG findings inconsistent with benign syndromes
 - ⊕ Partial seizure suggesting focal origin
 - ⊕ Unexplained neurological deficits on exam
 - ⊕ Age younger than 12 months
 - ⊕ If neuroimaging is performed, MRI is the modality of choice



MR Imaging Findings

MR findings in malformations of cortical development include:

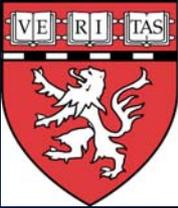
- ⊕ Focal or regional cortical thickening
- ⊕ Poor gray-white matter differentiation
- ⊕ Increased subcortical signal intensity on T2-weighted and fluid-attenuated inversion-recovery (FLAIR) sequences
- ⊕ Abnormal gyral anatomy



Menu of Tests: Specialized MRI Studies

Specific applications of MR for neurological disease:

- ⊕ **Functional MR (fMRI)** to localize brain functions based on changes in blood flow, as in presurgical mapping
- ⊕ **MR Spectroscopy (MRS)** for evaluation of local metabolism and tissue composition, as in pre- and post-treatment evaluation of brain tumors
- ⊕ **Magnetization prepared rapid acquisition gradient echo (MP-RAGE)** sequence can yield high-resolution T1-weighted images for more subtle abnormalities of cortical thickness and morphology

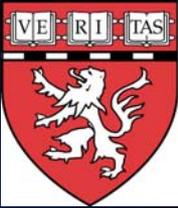


Menu of Tests: Lesser Used Studies

Other imaging modalities:

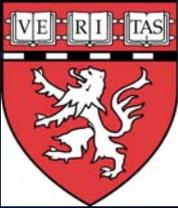
- ⊕ **Single Photon Emission Computed Tomography (SPECT)** to map brain perfusion in stroke and, in some cases, epilepsy
- ⊕ **Positron Emission Tomography (PET)** to image glucose metabolism, perfusion, and other functional markers in epilepsy and tumor recurrence
- ⊕ **Ultrasound** through the fontanelles for assessment of neonatal intracranial anomalies

Let's examine some examples of disorders caused by the disruption of specific steps in cortical development.



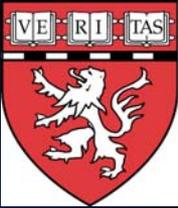
Tuberous Sclerosis Complex (TSC): A Disorder of Neuron Proliferation

- ⊕ A neurocutaneous syndrome resulting from an autosomal dominant mutation of TSC1 or TSC2 tumor suppressor genes
- ⊕ An important part of the differential diagnosis for subependymal (periventricular) dysplasia and for epilepsy



TSC: Results of Disordered Neuronal Proliferation

- ⊕ Brain manifestations include cortical hamartomas (tubers), subependymal nodules, white matter abnormalities, and heterotopic gray matter
- ⊕ These lesions result from abnormal gene expression in germinal matrix neuronal stem cells, with dysplastic cells then undergoing migration



Companion Patient 1: MRI in Tuberous Sclerosis

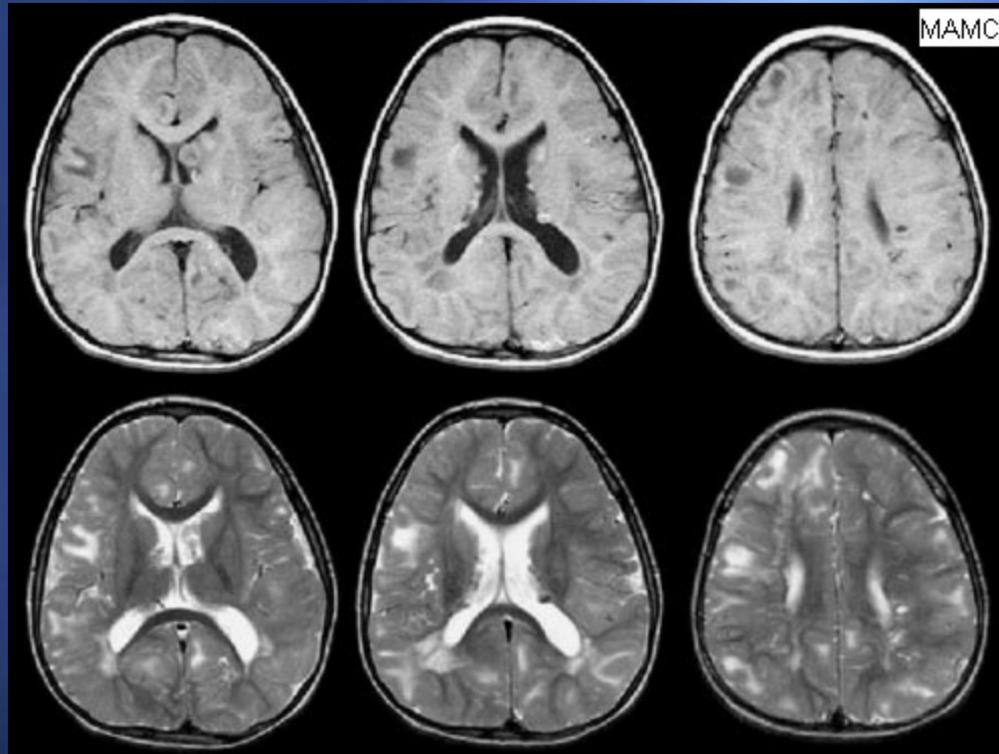
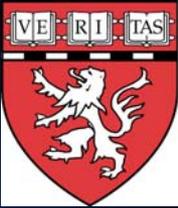


Image from Nick
Oldnall,
[http://www.e-
radiography.net/ibas
e5/Brain/index2.htm](http://www.e-radiography.net/ibas/e5/Brain/index2.htm)

Tubers appear hypointense on T1 and hyperintense on T2 and
FLAIR

- ⊕ Tubers in infants have the opposite properties because the surrounding white matter is unmyelinated; white matter lesions are also more visible at this age, making early imaging important

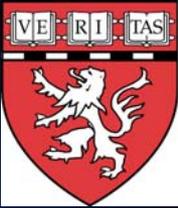
The next stage of cortical development is neuronal migration. This will be discussed in more depth, with examples from two index patients.



Our Patient MM: Presentation

MM is a 56yo right-handed woman with seizures since 1995.

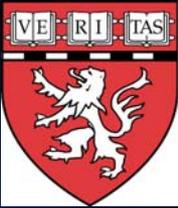
- ⊕ Initially diagnosed with epilepsy after two episodes of urinary incontinence
- ⊕ Episodes of dissociative feelings 2-4 times monthly lasting 5-20 seconds; no loss of consciousness, but no control of her activity
- ⊕ Episodes of apprehension lasting up to 2 minutes
- ⊕ Feeling of a "split" in her head or a "cloud"
- ⊕ Triggered by stress



Our Patient MM: Diagnosis

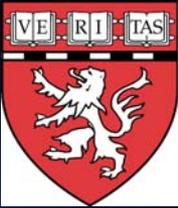
- ⊕ No history of generalized convulsions
- ⊕ As an adolescent, experienced daily episodes of déjà vu

Consistent with simple partial temporal lobe seizures, possibly since childhood



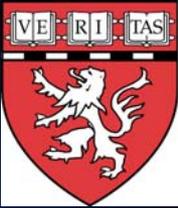
Our Patient MM: Further History

- ⊕ PMH: colon cancer in the setting of Lynch syndrome, possible Meniere's disease
- ⊕ FHx: No family history of seizures or other neurological problems



Our Patient MM: Initial Workup

- ⊕ MRI (outside hospital 1996):
 - ⊕ T2 signal abnormality in R posterior and frontal white matter
 - ⊕ Possible heterotopia R posterior temporal region
- ⊕ EEG:
 - ⊕ R frontotemporal spike and slow waves and sharp discharges



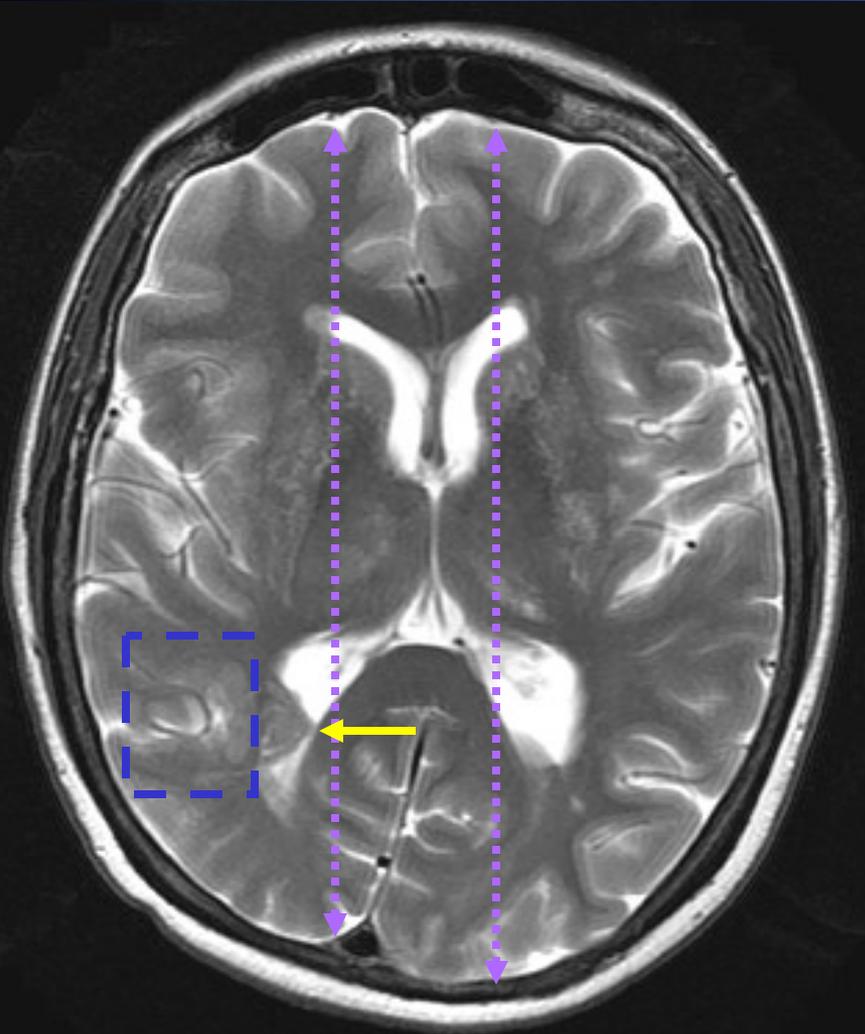
Our Patient MM: Course 2001-2008

Transferred care to BIDMC in 2001

- ⊗ Had been doing well on lamotrigine (Lamictal) and levetiracetam (Keppra)
- ⊗ Able to taper off lamotrigine to levetiracetam monotherapy
- ⊗ Tapered levetiracetam but seizure frequency increased so returned to 1500 qAM
- ⊗ On this dose, two more intense seizure episodes in 2008, including one episode of a formed visual hallucination of a person
- ⊗ Also in late 2008, new onset of headaches migrating across hairline, several times weekly, lasting minutes

Given the new symptoms of visual hallucination and headache, a new MRI was ordered.

Our Patient MM: Multiple Gray Matter Anomalies on MRI

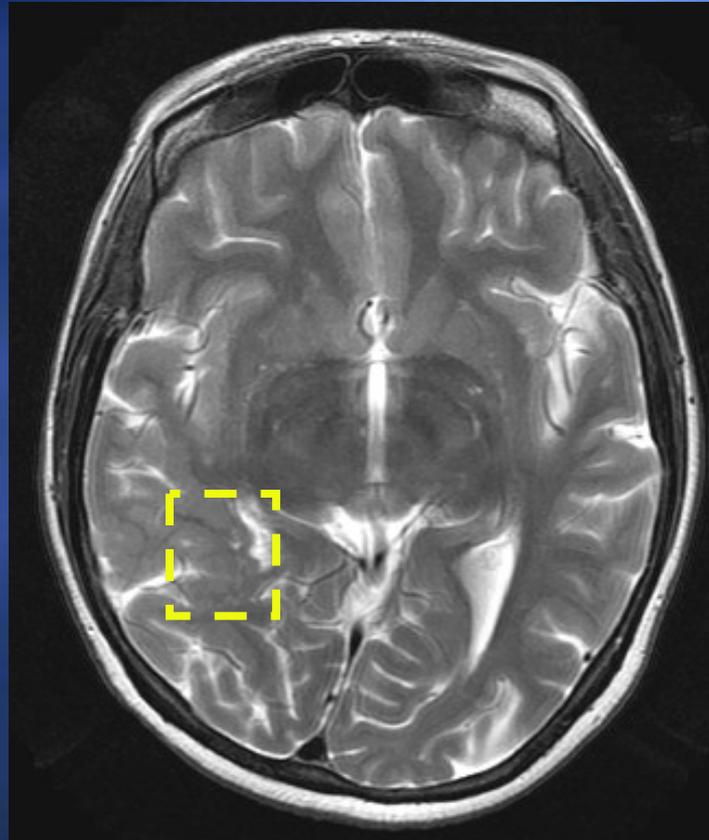
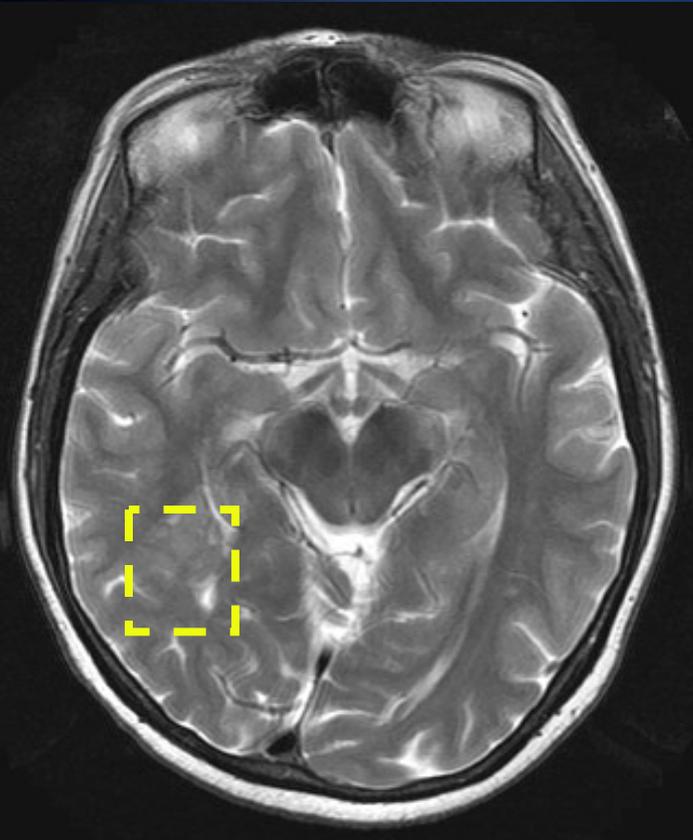


Axial T2-weighted MRI showing right temporal **subependymal heterotopia**, which projects into the occipital horn of the right lateral ventricle, is associated with **polymicrogyria** of the underlying cortex.

There is also right **hemimicrocephaly**.

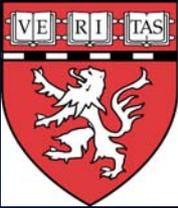
(PACS, BIDMC)

Our Patient MM: Subcortical Heterotopia on MRI



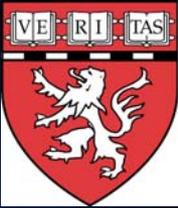
(PACS, BIDMC)

Axial T2-weighted MRI -- There is also another **focus of gray matter signal** inside the subcortical white matter of the right temporal lobe which might represent subcortical heterotopia.



Our Patient MM: Clinical Outcome

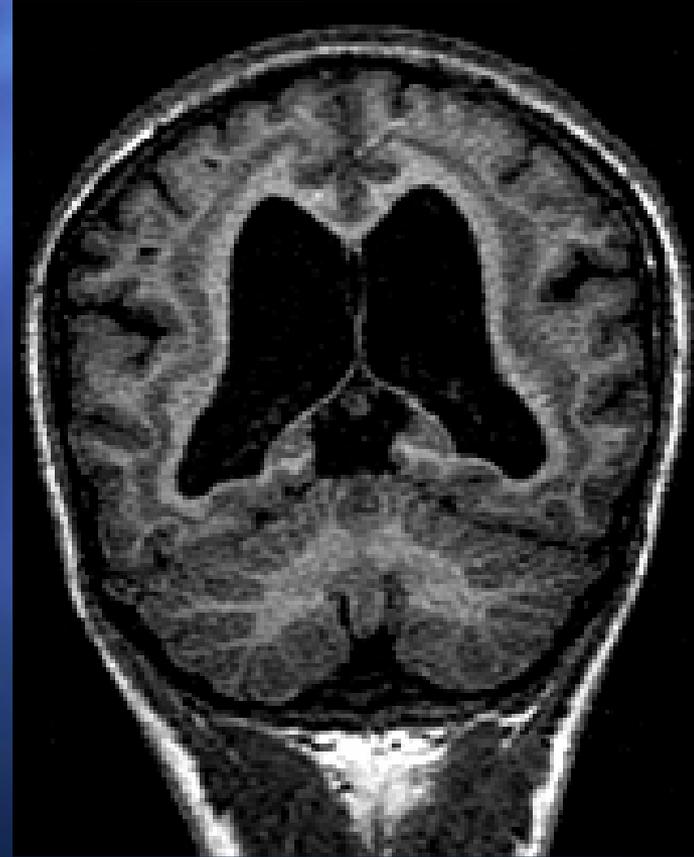
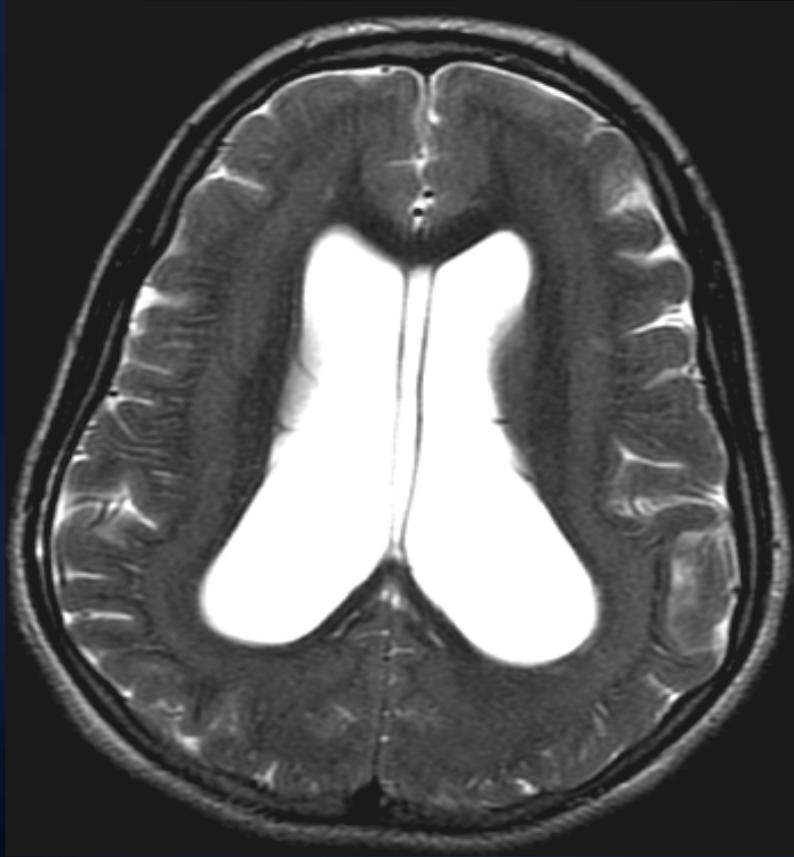
- ⊕ No mass lesion or enhancing soft tissue was found that would be concerning in the context of new seizure symptoms and headaches.
- ⊕ Despite significant abnormalities on neuroimaging, MM's neurological issues seem to be mild and relatively stable. She will follow up after six months.



Heterotopia: A Disorder of Neuron Migration

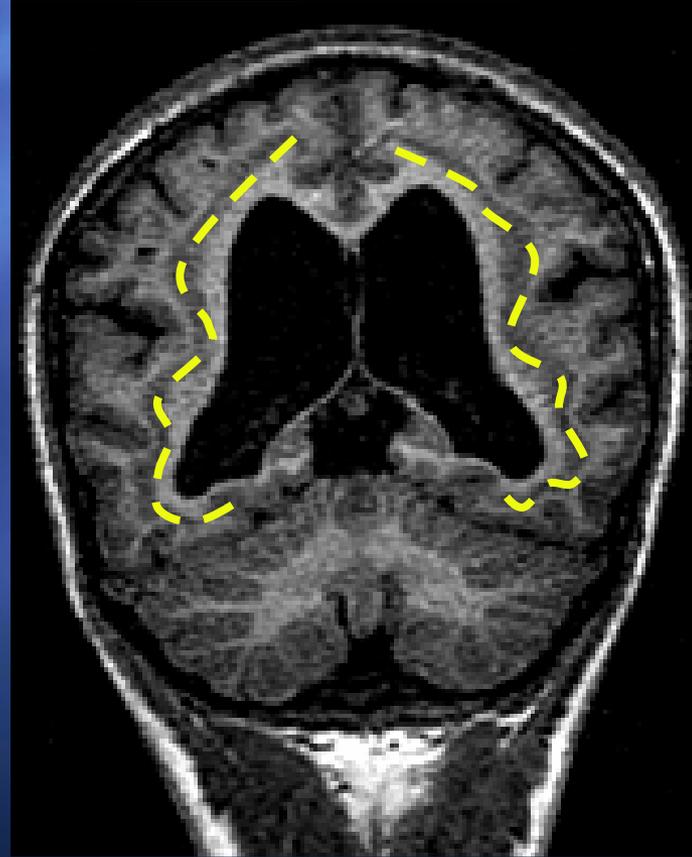
- ⊕ Gray matter heterotopias are malformations due to abnormal neuronal migration
- ⊕ Types:
 - ⊕ Band (“double cortex”)
 - ⊕ Subcortical
 - ⊕ Subependymal (periventricular)

Companion Patient 2: Abnormal Gray Matter on MRI



Axial T2-weighted and coronal T1-weighted MRI

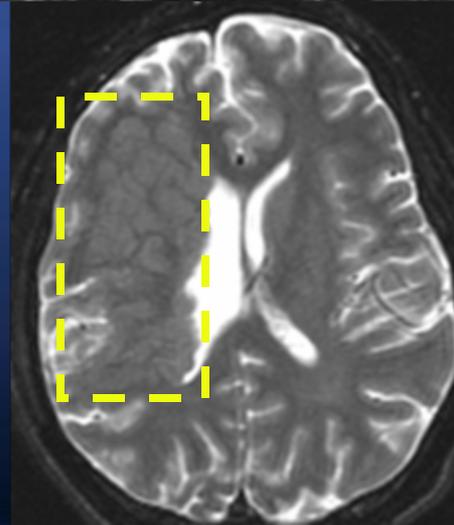
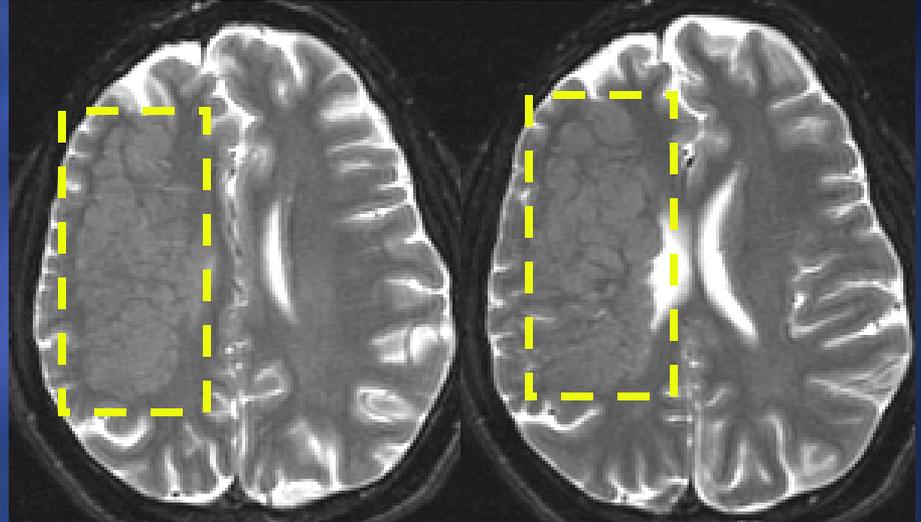
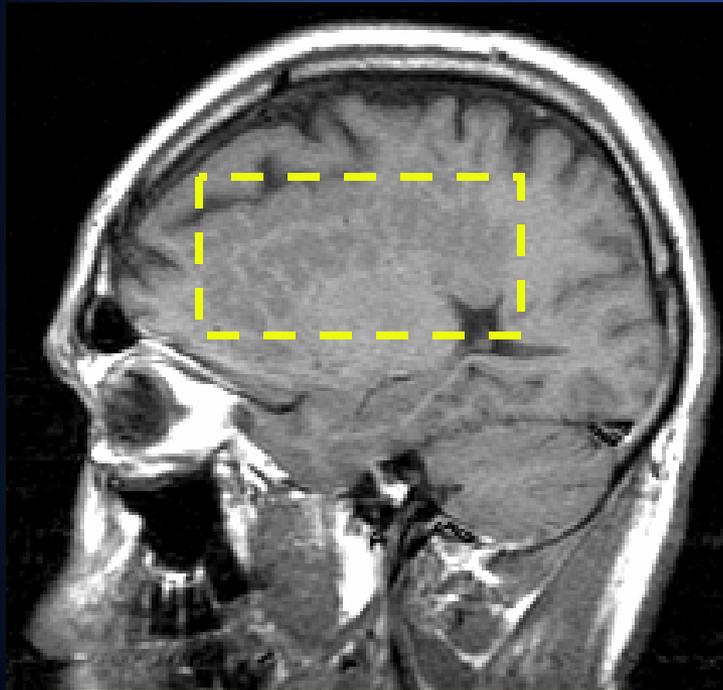
Companion Patient 2: Band Heterotopia on MRI



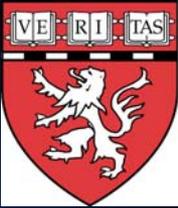
Axial T2-weighted and coronal T1-weighted MRI – Can you see why band heterotopia is sometimes called “double cortex”?

Images courtesy of Dr. Moonis

Companion Patient 3: Subcortical Heterotopia on MRI



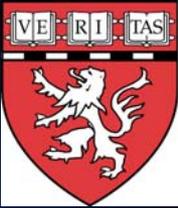
For an example of subependymal heterotopia, and of the implications of finding gray matter heterotopias through neuroimaging, we will now turn to a pediatric patient.



Our Patient DP: Presentation

DP is a 2-year-old female with complex partial seizures since age 11 months who presents to the Children's Hospital Epilepsy Program.

- ⊕ Seizures characterized by cessation of activity, staring, lip puckering, swallowing, gulping, a frightened look, and clawing of the hands.
- ⊕ Duration one to two minutes, in clusters of five to twenty seizures in 24 hours every few weeks
- ⊕ Normal EEGs x3, normal CT



Our Patient DP: Further History and Exam

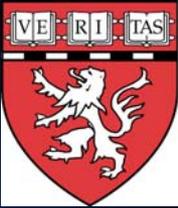
PMH: Normal gestation, normal delivery at term.
Developmental milestones met on time.

FHx: Mother with depression, anxiety, and ADHD. No family history of birth defects or seizures

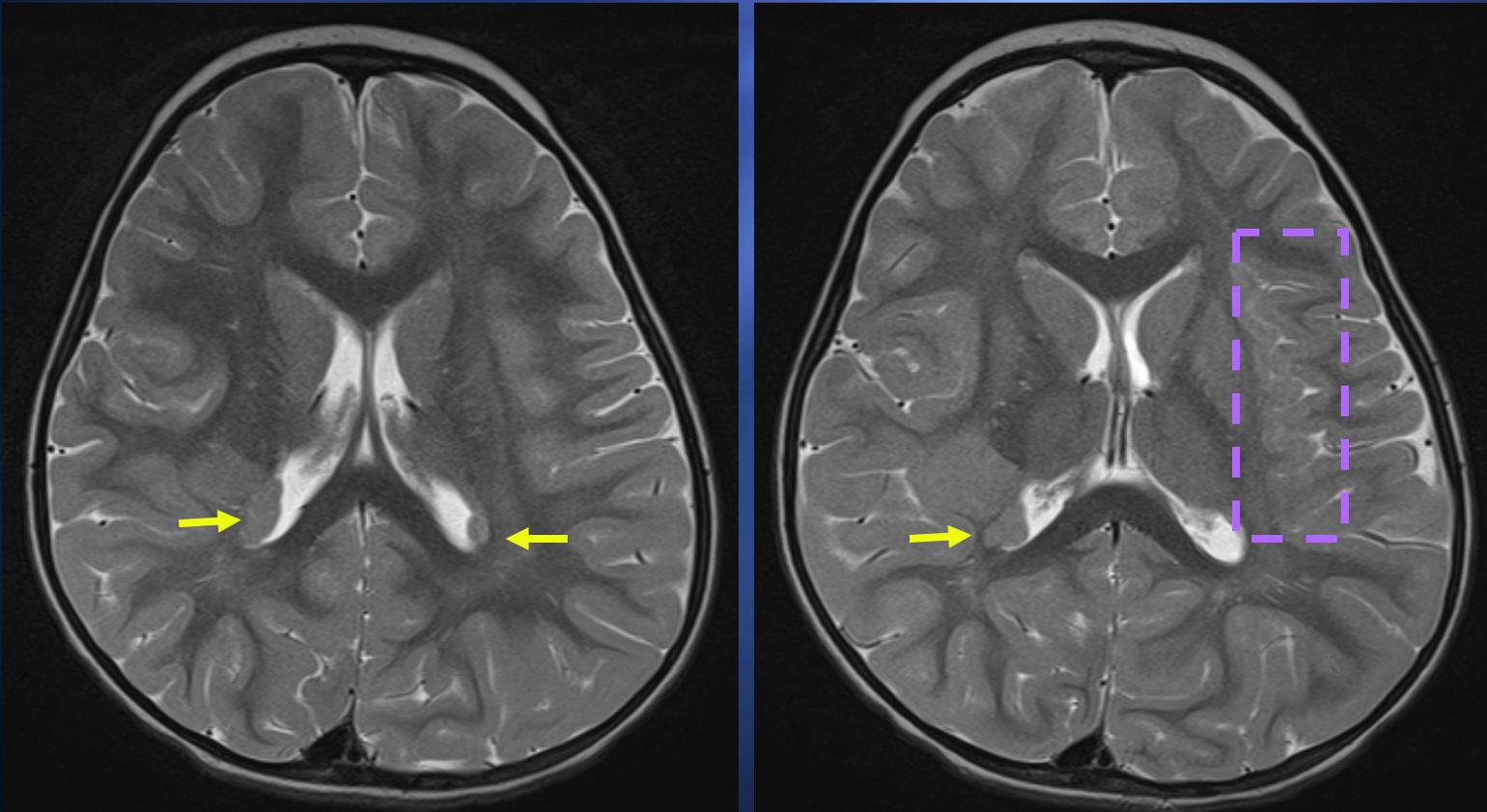
⊕ Benign infantile seizures often have a positive family history

Physical Exam: No dysmorphic features, no hypo- or hyper-pigmented skin lesions. Normal neurological exam.

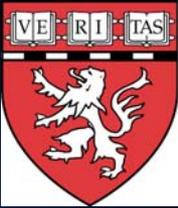
DP carried an outside diagnosis of benign partial epilepsy with affective symptomatology. However, given the partial seizures, an MRI was obtained.



Our Patient DP: Subependymal Heterotopia on MRI

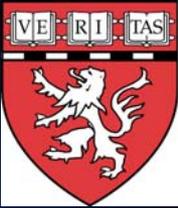


Axial T2-weighted images showing **nodules of gray matter signal** near the lateral ventricles bilaterally, as well as **thickening of the insular cortices** consistent with heterotopic gray matter/cortical dysplasia (Children's Hospital)



Our Patient DP: Implications of Subependymal Heterotopia

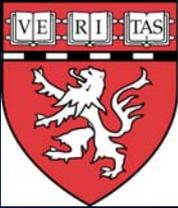
- ⊕ The MRI was discussed with DP's parents. The findings likely explain DP's seizures, and also suggest that she is less likely to outgrow them, unlike benign partial epilepsy of infancy.
- ⊕ Although children with periventricular heterotopia may be seizure-free for several years off medication, treatment with oxcarbazepine (Trileptal) would be a good choice for DP. It is a narrow-spectrum agent (for partial seizures only, i.e. with focal epileptogenic lesions like hers) with a favorable side effect profile.



Our Patient DP: A Potential Genetic Cause For Her Findings

- ⊕ Testing for a filamin-A (FLNA/FLN1) single gene mutation was recommended.
 - ⊕ Filamin proteins are involved in the formation of the filopodia that allow neurons to migrate along the glial scaffolding.
 - ⊕ FLNA mutations are X-linked; heterozygous females have periventricular heterotopia, and homozygous males die in utero.
 - ⊕ If DP is a heterozygote, her mother could also undergo genetic testing and MRI. This may be contributing to her mother's neuropsychiatric history.

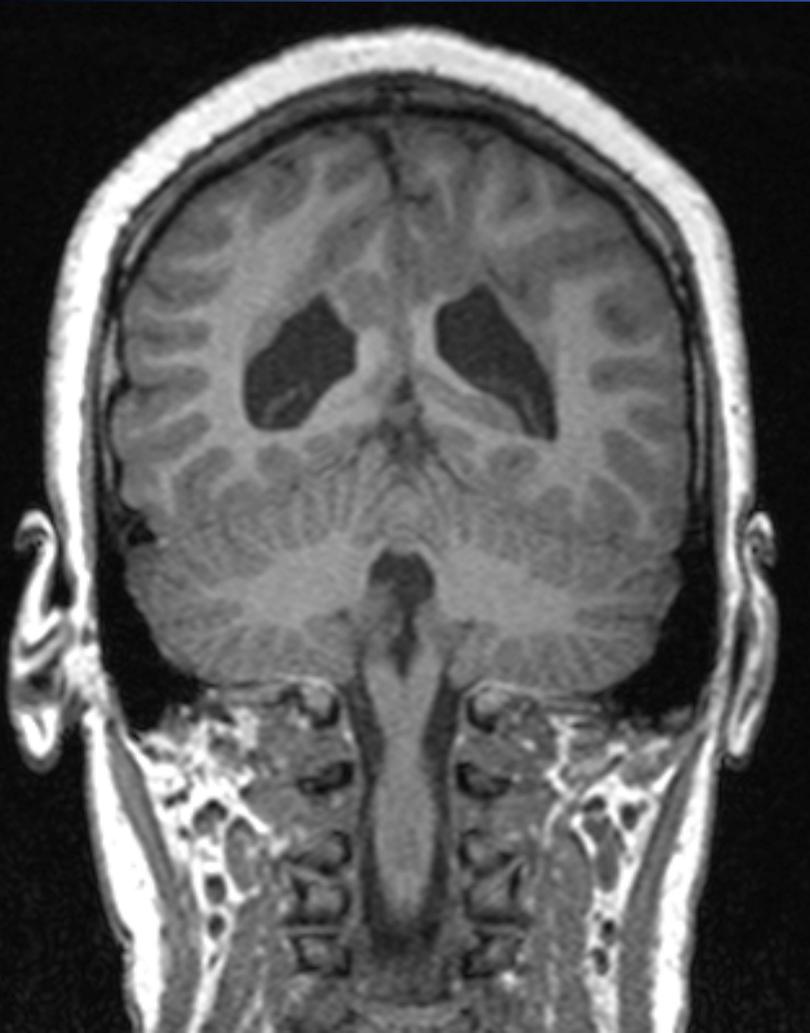
We will briefly discuss disruptions of the last step in cortical development, cortical organization.



Schizencephaly: A Disorder of Cortical Organization

- ⊕ Associated with polymicrogyria (many small gyri)
- ⊕ Clefts extending from the pial surface to the lateral ventricle
- ⊕ Clefts lined with polymicrogyric cortex with abnormal lamination

Companion Patient 4: An Abnormal Cleft in the Cortex



10-year-old boy with history of hyperreflexia, developmental delay, microcephaly, two year history of intermittent left leg weakness.

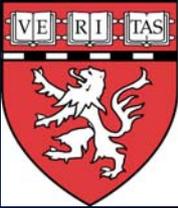
Companion Patient 4: Schizencephaly on MRI



MRI showed closed lip schizencephaly in the bilateral parietal occipital regions with associated dysplastic grey matter and bilateral subependymal heterotopia.

See one **example of a cleft** on this coronal T1-weighted MP-RAGE image.

(Children's Hospital)



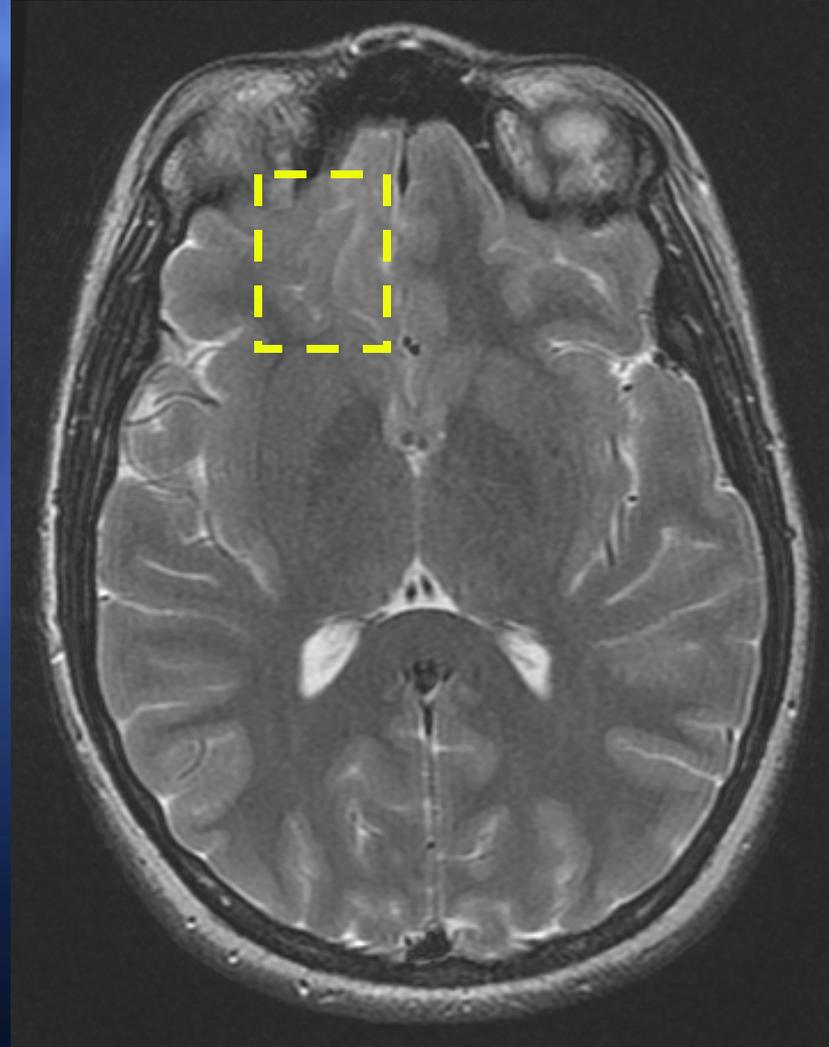
Focal Cortical Dysplasia

- ⊕ Confusing terminology: generally refers to a milder subset of the malformations of cortical development, which may result from perturbations of neuron **proliferation** *and/or* cortical **organization**
- ⊕ Separately classified as:
 - ⊕ Type I: architectural abnormalities
 - ⊕ Type II (Taylor type): architectural abnormalities and dysplastic neurons
 - ⊕ IIa: without balloon cells
 - ⊕ IIb: with balloon cells

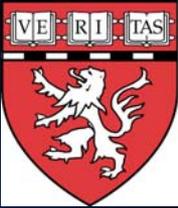
Companion Patient 5: Focal Cortical Dysplasia on MRI

16 year old girl with seizures

Axial T2-weighted image showing **patchy irregular T2 prolongation** in the inferior right frontal cortex with associated abnormal gyral pattern and white matter, consistent with focal cortical dysplasia.

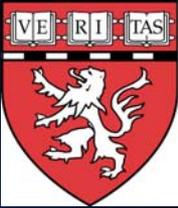


(Children's Hospital)



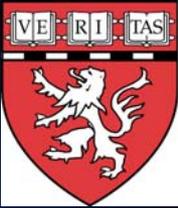
Key Points

1. Malformations of cortical development reflect embryological disruptions in:
 - ⊠ Neuronal proliferation (ex. TSC)
 - ⊠ Neuronal migration (ex. heterotopias)
 - ⊠ Cortical organization (ex. schizencephaly)
 - ⊠ Multiple steps (ex. focal cortical dysplasia)
2. These lesions are important causes of refractory epilepsy.



Key Points II

3. MRI is the preferred imaging study for malformations of cortical development, with extensive information available from newer sequences and MR modalities.
4. Neuroimaging of these lesions is important for diagnosis and management decisions in epilepsy, including the feasibility and likely success of surgical resection in cases that are refractory to medication.

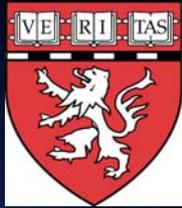


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Dr. Gillian Lieberman and Maria Levantakis



References

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- ⊕ Barkovich AJ, et al. A developmental and genetic classification for malformations of cortical development. *Neurology* 2005;65:1873-1877.
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