Supratentorial Brain Malformations

Edward Yang, MD PhD
Department of Radiology
Boston Children’s Hospital
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Disclosures:

Consultant, Corticometrics LLC
Objectives

1) Review major steps in the morphogenesis of the supratentorial brain.

2) Categorize patterns of malformation that result from failure in these steps.

3) Discuss particular imaging features that assist in recognition of these malformations.

4) Reference some of the genetic bases for these malformations to be discussed in greater detail later in the session.
Overview

I. Schematic overview of brain development

II. Abnormalities of hemispheric cleavage

III. Commissural (Callosal) abnormalities

IV. Migrational abnormalities
   - Gray matter heterotopia
   - Pachygyria/Lissencephaly
   - Focal cortical dysplasia
   - Transpial migration
   - Polymicrogyria

V. Global abnormalities in size (proliferation)

VI. Fetal Life and Myelination Considerations
I. Schematic Overview of Brain Development
Embryology

Closed Neural Tube (4 weeks)

Hemispheric Cleavage (4-6 weeks)

Ventricular/Subventricular Zones

Neuronal Precursor Generation (Proliferation) (6-16 weeks)

Cerebral Hemisphere

Neuronal Migration Ventricle → Cortex (8-24 weeks)

Callosum Formation Genu → Splenium (11-20 weeks)

Corpus Callosum

Top        Mid-sagittal
Embryology

From ten Donkelaar
Clinical Neuroembryology 2010
II. Abnormalities of Hemispheric Cleavage
Holoprosencephaly (HPE)

Imaging features:
Incomplete hemispheric separation +

1) No septum pellucidum in any HPEs

2) Falx and callosum range from absent (alobar) to present posteriorly (semilobar, lobar)

3) Deep gray matter fused to varying degrees: total fusion (alobar) to largely separated

4) Lateral ventricles abnormal: monoventricle often with dorsal cyst (alobar), temporal horns (semilobar), frontal horns (lobar)

5) Third ventricle absent (alobar) to small (semilobar) to fully formed (lobar)

6) Azygous anterior cerebral arteries

7) Face (disability) follows brain: hypotelorism, midface dysraphism, single median maxillary central incisor (SMMCI), pyriform aperture stenosis, probiscus, cyclopia seen in more severe holoprosencephalies (alobar)

Etiologies:
Aneuploidy (25-50%): (13^3>18^3), CNVs
Single gene (25%): SHH, Zic2, Six3, TGIF
Syndromic: Smith-Lemli-Opitz, Pallister Hall, Rubinstein Taybi
Environment: maternal diabetes, teratogen

Petryk WIREs Dev Biol 2015
Winter Radiographics 2015
Alobar HPE

Single continuous pancake lobe
Deep gray matter fusion
Absent olfactory apparatus
Monoventricle with rudimentary third ventricle + large dorsal cyst
Absent: CC, septum, falx
Semilobar HPE

Fused hemispheres and gray matter
Rudimentary splenium
Defined temporal horns but incompletely formed hippocampus
Absent: falx, anterior CC, septum
Olfactory apparatus present
Lobar HPE

Posterior half of the CC is present
Falx is present posteriorly
Posterior cerebrum cleaved and deep gray less fused
Frontal and temporal horns defined; hippocampi formed
Absent: septum pellucidum
Lobar HPE

At least posterior half of the CC is present
Falx is present posteriorly
Posterior/Dorsal cerebrum cleaved but deep gray still fused
Frontal and temporal horns defined; hippocampi formed
Absent or truncated: septum pellucidum
Middle Interhemispheric Variant (Dorsal) HPE

Segmental disruption of the corpus callosum where fused
Coronally oriented sylvian fissures
Basal ganglia fusion (3rd ventricle obliteration) and hypotelorism uncommon; can have thalamic fusion
Reportedly malformations of cortical development (MCD) in up to 86%
Sx: spasticity, DD similar to lobar HPE but much lower endocrine, movement d.o morbidity

Simon AJNR 2002
HPE Facial anomalies

Hypotelorism: 28 wk OOD @ 32 weeks

Solitary Median Maxillary Central Incisor + Pyriform Aperture Stenosis

Single nares @ 22 weeks
Septo-preoptic HPE

Proposed variant of Lobar HPE

- fusion restricted to septal/preoptic region (fornix fusion, mild pACC)
- azygous ACA common
- midface anomalies: pyriform aperture stenosis & solitary maxillary incisor > 70%

Hahn, Barnes et al. AJNR 2010

6 day old with upper airway obstruction

SMMC1 + pyriform aperture stenosis
Septo-optic dysplasia

Clinical syndrome consisting of vision impairment + endocrine dysfunction

- Imaging:
  - absent septum pellucidum w/intact CC
  - small optic nerves (88% bilateral)
  - Small pituitary, ectopic posterior pituitary
  - Fused midline fornices with “pointing” of inferior frontal horns
  - Variable: deficient olfactory apparatus, schizencephaly, PMG (up to half)
  - → mild ventral forebrain malformation, mild lobar HPE variant according to some

14F with endocrine deficiency, visual loss (5/125) for V/HA

Sag T1  Ax T1  Cor T2
Septo-optic dysplasia

Clinical syndrome consisting of vision impairment + endocrine dysfunction

- Imaging:
  - absent septum pellucidum w/intact CC
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  - Variable: deficient olfactory apparatus, schizencephaly, PMG (up to half)
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17M with HA after roll-over MVA during vacation

*note schizencephaly is a morphology not a mechanism:
Migrational versus post-insult
Septo-optic dysplasia: Inverse Approach

Clinical syndrome consisting of vision impairment + endocrine dysfunction
- Can be diagnosed w/ septum pellucidum, w/o other (e.g. olfactory hypoplasia)
- May have other abnormalities in isolation: e.g. HesX1 mutation
  - 3/16 cases tabulated in one case series had absence of the septum
  - Other abnormalities (depending on mutation)
    - ectopic posterior pituitary
    - pituitary hypoplasia
    - unilateral or bilateral optic nerve hypoplasia
    - Colobomata, optic disk dysplasia
    - olfactory apparatus (in mice)

4mo with optic hypoplasia and endocrine insufficiency/sepsis, heterozygous pathogenic Hesx1 mutation

Mehta Clinical Endocrinology 2009
Dattani Nature Genetics 1998
Corneli J. Endocrinol Invest 2008
Hypothalamic fusion anomaly

Isolated fusion of two halves of the hypothalamus (GM intensity)
- In our experience see often as an incidental at 3T
- Published experience questions whether this represents a form of HPE due to co-occurrence with palate abnormalities and PF malformations

Whitehead AJNR 2014

10F PVL and new seizures

16M with facial palsy and suspected Lyme
III. Commissural (Callosal) Abnormalities
Embryology

Callosum Formation
Genu → Splenium
(11-20 weeks)

Edwards Brain (2014)
Normal Commissures

Corpus Callosum (CC): rostrum, genu, body, isthmus, splenium (5)
Anterior Commissure (AC)
Hippocampal Commissure (HC)

8M with suspected retropharyngeal abscess
Classic Agenesis of the Corpus Callosum (ACC)

Complete failure of callosal formation
- tricommissural agenesis (AC, HC, CC) most common
- 45% with associated abnormality (cyst, DWM, MCD)

Imaging findings:
- Colpocephaly and hippocampal malrotation
- Parallel configuration of ventricles
- Absence of cingulate sulcus: gyral folds radiate to high 3rd ventricle
- Redirection of white matter tracts along lateral ventricles (Probst bundles)

4mo with ventriculomegaly:
Tri-commissural agenesis
Classic Agenesis of the Corpus Callosum (ACC)

Complete failure of callosal formation
- tricommissural agenesis (AC, PC, CC) most common
- 45% with associated abnormality (cyst, DWM, MCD)

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- Redirection of white matter tracts along lateral ventricles (Probst bundles)

13mo with fetal ACC diagnosis, mild DD: bicommissural ACC
Partial Agenesis (Dysgenesis) of the Callosum (pACC)

Incomplete formation of the 5 corpus callosum segments
- generally order of formation reflects definition in utero
  genu → body → isthmus → splenium → rostrum
- may not be embryologically rigorous explanation

Narrative generally works though:

- 5F PMG, interhemispheric cysts
- 12F seizures, callosal lipoma
- 14mo M FTT
- 6mo F infantile spasm
Hypoplasia of the Callosum

Complete formation of all callosal segments but decreased volume
- exclude prior injury as an explanation

Callosal abnormalities have low penetrance
- fully formed CC, hypoplasia, pACC, and ACC can all be seen 2/2 in some single gene disorders

When in question: Garel AJNR 2011 (normative CC measures)

12F facial dysmorphism
15mo M global DD
5q14 (MEF2C) deletion
5do with trisomy 13
Abnormal Callosum: exception to narrative

Sag T1

Semilobar HPE

Sag T1+C

MIHV HPE

Sag T1

9M w/ prune belly and headache
-ruptured mycotic aneurysm in endocarditis

19mo M Developmental Regression
-segmental deficiency
-no evidence prior injury
Other commissural abnormalities

Excessively thick corpus callosum
- normal variant
- Neurofibromatosis
- Megalencephaly syndromes

18F w/ episode amaurosis fugax
4M NF1 and optic pathway glioma
3M MCAP syndrome
Other commissural abnormalities

Anterior commissure: thickening or hypoplasia

3M with expressive language delay

9F Congenital Fibrosis Extraocular Muscles (TUBB3)
Genetics of Commissural Abnormalities (ACC, pACC, hypoplasia)

**Disorders of Proliferation**

Microcephaly + ACC

- ASPM (MCPH2)  
- WDR62 (MCPH5)  
- 1q42-q44 (AKT3)  

Macrocephaly + ACC

- NSD1/NFIX (Soto sx)

**Midline patterning**

- Apert syndrome 23%?
- Joubert/ciliopathies 10%

**Migrational Disorders**

- RELN Lissencephaly -33%
- TUBA1A Lissencephaly -50%
- NDE microcephaly/lissencephaly -67%
- TUBB2B PMG -100%
- ARX microcephaly/MR -100%
- TUBB3 CFEOM, PMG, Lis -25% (hypoplasia inc)
- ACTB/ACTG (Baraitser-Winter) "uncommon"
- DCX/FLNA "common"
- L1 syndrome (CRASH)

**Miscellaneous**

- Alcohol
- Lipoma associated?

→ 30-45% ACC have a genetic explanation with a minority being single gene

III. Migrational Abnormalities
Embryology

Neuronal Precursor Generation (6-16 weeks)

Neuronal Migration
Ventricle → Cortex (8-24 weeks)

Ventricular/Subventricular Zones
Cortical Migration

7 weeks
- Preplate

8-13 weeks
- Ventricular Zone/Germinal Matrix
- Subplate ("VII")
- Marginal Zone (I)

13-24 weeks
- Subventricular/Intermediate Zones
- Cortical Layer (VI)
- Cortical Layer (V)
- Mature Ependyma
- Mature Deep White Matter
- Cortex

24 weeks
- 27 - 29 weeks
- 33-34 weeks
Cortical Migration

- 20 weeks at 3T
- 24 weeks

- Cortex
- Subplate
- Subventricular/Intermediate Zone
- Ventricular Zone/Germinal Matrix
- Cortex
Migrational/Organizational* Abnormalities

- GM heterotopia
- Pachygyria/Lissencephaly (LIS)
- Focal Cortical Dysplasia (FCD)
- Polymicrogyria (PMG)
- Overmigration (COBLIS)

Neuronal Migration/Organization
Ventricle → Cortex
(8-24 weeks)

Guerrini *Lancet Neurology* 2014
Barkovich *Brain* 2012
**Imaging Technique for MCD**

For seizure or suspected structural abnormality, 3T w/ 32-64 channel head coil

- Intermediate myelination can obscure abnormalities at 6-24 mo of age
- 7T or directed high resolution imaging may help (De Ciantis AJNR 2014)
- options: magnetization transfer T1 (FCD), SWI, contrast

- MPRAGE, IR-SPGR
  - ~1mm isotropic

- Ax FSE T2
  - 0.4 x 0.5 x 2.5/0 mm, NEX2

- Cor FSE T2
  - 0.4 x 0.5 x 2.5/0 mm, NEX2

- SMS DTI
  - 35 dir B=1000, 1.5-2mm

- Ax FLAIR
  - 0.6 x 0.6 x 4/1mm

- Sag FLAIR SPACE
  - ~1mm isotropic

- T2 SPACE/CUBE FLAIR
  - ~1mm isotropic

- PASL
  - Perfusion

IV. Migrational Abnormalities
- **Gray matter heterotopia**
- Pachygyria/lissencephaly
- Focal cortical dysplasia
- Transspial migration
- Polymicrogyria
GM Heterotopia: Classification

Normal neurons in abnormal locations
-may or may not have laminated structure like cortex

Classified by location/morphology:
- Periventricular Nodular or Subependymal GM Heterotopia (PVNH/SEGMH)
- Subcortical
- Subcortical *
- Transmantle
- Band (to be discussed w/pachygyria)
**Periventricular Nodular Heterotopia (PVNH)**

Most common and best characterized GM heterotopia, historically 80+% w/ epilepsy*

**Etiologies:**  Watrin *CNS Neurosc.&Therapeutics* 2014

- **FLNA (Xq28):** said to account for 100% familial X-linked bil. PVNH, 26% sporadic
  - mass-like, confluent PVNH sparing temporal horns, PF anomalies
  - majority female (males may be somatic mutants)
  - associated cardiac disease (valvular, PDA), hyperextensibility, PF abnormalities

- **ARFGEF2 (20q13):** microcephaly, delayed myelination

**Other:**  *C6orf70 (6q26), FAT4 (4q28), DCHS1 (11p15), CNV @ 5q14?*

**Imaging:**  Gonzalez *AJNR* 2013

- PVNH 79% bilateral
- **Posterior PVNH:** MCD 52% (14% anterior, 28% diffuse)+ PF malformations (32-38%)
- **Unilateral PVNH:** MCD 52% (27%, bilateral PVNH)
- **Diffuse PVNH:** CC anomalies 82% + mega cisterna magna 31%

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15F with h/o seizures, headache

6F with migraines
PVNH or not PVNH

Should follow gray matter signal

6F with migraines

15mo F observed @ OSH for PVNH after hydrocephalus eval
PVNH or not PVNH

Should follow gray matter signal

6F with migraines

15mo F observed @ OSH for PVNH after hydrocephalus eval

1 year f/u: anaplastic ependymoma (WHO III)
PVNH or not PVNH

Should follow gray matter signal

4F w/ Tuberous sclerosis: PVNH + subependymal nodules
Other GM Heterotopia

7M with headaches: small subcortical

7M with headaches: mass-like subcortical

Newborn w/ missing thumbs/MCA: curvilinear subcortical

5M with HLH: transmantle GMH

Barkovich AJNR 2000
IV. Migrational Abnormalities
- Gray matter heterotopia
- Pachgyria/lissencephaly
- Focal cortical dysplasia
- Transpial migration
- Polymicrogyria
Pachygyria/Lissencephaly (LIS)

Definitions:
- lissencephaly/agyria: absence of sulcation w/cortical thickening
- pachygyria: sulcation diminished but present, attenuated lissencephaly;
- subcortical band heterotopia (SBH): GM heterotopia below 6-layer cortex

Morphologic (Dobyns) Classification:

1. Agyria
2. Mostly agyria
   -a temporal
   -b occipital
3. Agyria – pachygyria gradient
4. Pachygyria
5. Pachygryria + SBH
6. Subcortical band heterotopia

a- posterior more severe
b- anterior more severe

Reproduced from Fry AJMG-C 2014
Pachygyria/Lissencephaly (LIS)

Genetic Etiologies: many mutations concerning cytoskeletal mechanics

**Posterior > Anterior**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>LIS3-4, (+YWHAE: LIS1-2 Miller-Dieker syndrome)</th>
<th>LIS1-4, cerebellar hypoplasia, BG abnormal, PMG(L)</th>
<th>LIS4-6, BG abnormal</th>
<th>LIS3, cerebellar hypoplasia, BG abnormal, PMG(L)</th>
<th>LIS3-4</th>
<th>LIS4; ambiguous genitalia, male, ACC, BG abnormal</th>
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<td>LIS1 (17p13)</td>
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<td>TUBA1A (12q13)</td>
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<td>TUBB2A (6p25)</td>
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<td>TUBB2B (6p25)</td>
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<td>TUBG1 (17q21)</td>
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<td>DYNC1H1 (14q32)</td>
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<td>KIF2A (5q12)</td>
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<td>ARX (Xq22)</td>
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Guerrini & Dobyns Lancet Neuro 2014; Kato & Dobyns HMG 2003; Cushion AJHG 2014

90 do w/ Miller-Dieker Sx

7 do w/ TUBA1A
Pachygyria/Lissencephaly (LIS)

Genetic Etiologies: many mutations concerning cytoskeletal mechanics

**Posterior > Anterior**

- **LIS1 (17p13)**
  - LIS3-4, (+YWHAE: LIS1-2 Miller-Dieker syndrome)

- **TUBA1A (12q13)**
  - LIS1-4, cerebellar hypoplasia, BG abnormal, PMG(L)

- **TUBB2A (6p25)**
  - LIS4-6, BG abnormal

- **TUBB2B (6p25)**
  - LIS3, cerebellar hypoplasia, BG abnormal, PMG(L)

- **TUBG1 (17q21)**
  - LIS3-4

- **DYNC1H1 (14q32)**
  - LIS4

- **KIF2A (5q12)**
  - LIS4

- **ARX (Xq22)**
  - LIS2-4; ambiguous genitalia, male, ACC, BG abnormal

**Newborn w/ TUBA1A**

**90do w/ Miller-Dieker Sx**
Pachygyria/Lissencephaly (LIS)

Genetic Etiologies: many mutations concerning cytoskeletal mechanics

Anterior > Posterior
- DCX (Xq23)
- RELN (7q22), VLDLR (9p24)
- ACTB (7p22), ACTG1 (17q23)

LIS1-4 (male) LIS6/SBH (female)
LIS3-4 + Cerebellar Hypoplasia
LIS4-5 Baraitser Winter Sx

2F w/ DCX mutation
DD, seizure

9M w/ DCX mutation
epilepsy
Pachygyria/Lissencephaly (LIS)

Genetic Etiologies: many mutations concerning cytoskeletal mechanics

Anterior > Posterior

DCX (Xq23)
RELN (7q22), VLDLR (9p24)
ACTB (7p22), ACTG1 (17q23)

LIS1-4 (male) SBH (female)
LIS3-4 + Cerebellar Hypoplasia
LIS4-5 Baraitser Winter Sx

Dol 0 Baraitser-Winter (ACTG1) atypical: P>A, ACC, Cbl Hypo
Pachygyria/Lissencephaly: attenuated phenotypes

Even with focal pachygyria, can be assisted with DTI

2F seizures, ACC, PVNH, transmantle heterotopia, pachygyria versus cobblestone LIS
IV. Migrational Abnormalities
-Gray matter heterotopia
-Pachygyria/lissencephaly
-**Focal cortical dysplasia**
-Transpial migration
-Polymicrogyria
Focal Cortical Dysplasia (FCD)

Focal areas of cortical disorganization (ILAE 2011)
- **FCD I**: disruption of normal layers/lamination and columnar organization
- **FCD II**: co-occurring dysplastic neurons, heterotopic foci in WM
- **FCD III**: FCD I + other epileptic lesion (e.g. mesial temporal sclerosis)

FCDs account for 75% of refractory epilepsy presenting for resection
- ~60% seizure free after surgery with FCD (similar to MTS or other lesion)
- 30-40% seizure free without lesion

➔ FCD detection therefore a major focus of epilepsy evaluation
- 36% of path proven cases have no MR abnormality
- 68% ictal surface EEG abnormality

Bluemcke *Epilepsia* 2011
Lerner *Epilepsia* 2009
Jobst *JAMA* 2015
Focal Cortical Dysplasia (FCD)

Imaging Features:
- FCD I/II: cortical/subcortical signal increase, blurring
- FCD I: generally smaller or “normal”
- FCD II: cortical thickening, modest gyral expansion
  - transmantle sign: 91% IIb vs 56% IIa

6F with intractable seizures & F4 spikes: FCD IIb @ resection
Focal Cortical Dysplasia (FCD)

Imaging Features:
- FCD I/II: cortical/subcortical signal increase, blurring
- FCD I: generally smaller or “normal”
- FCD II: cortical thickening, modest gyral expansion
  - transmantle sign: 91% IIb vs 56% IIa

Tubers in TS histologically identical to FCD IIb
- Points to genetic etiology
- Somatic TSC1/2, PTEN, DEPDC5, mTOR mutations
- Conversely, TS occasionally dx for single FCD IIb
Focal Cortical Dysplasia (FCD)

Imaging Features:
- FCD I/II: cortical/subcortical signal increase, blurring
- FCD I: generally smaller or “normal”
- FCD II: cortical thickening, modest gyral expansion
  - transmantle sign: 91% IIb vs 56% IIa

8F intractable epilepsy: FCD IIb
- gyral swelling, cortical infiltration
- lack of tapering tail

30mo M intractable epilepsy: FCD IIa
Focal Cortical Dysplasia (FCD)

Imaging Features:

- FCD I/II: cortical/subcortical signal increase, blurring
- FCD I: generally smaller or “normal”
- FCD II: cortical thickening, modest gyral expansion
  - transmantle sign: 91% IIb vs 56% IIa

14M w/ intractable seizure (left hand paresthesia, left facial numbness, speech arrest): FCD Ia

9F with left temporal electroclinical seizures: FCD IIIa
Anterior lobectomy and seizure free x 3 yr
Focal Cortical Dysplasia (FCD)

Imaging Features:
- FCD I/II: cortical/subcortical signal increase, blurring
- FCD I: generally smaller or “normal”
- FCD II: cortical thickening, modest gyral expansion
  - transmantle sign: 91% IIb vs 56% IIa

Importance of clinical correlation and good imaging

4F with high pitched sound preceding speech arrest; left mid-temporal seizure: FCD IIa
20M Ivy League student with lesion detected for HA @ 4yo, subsequently CPS (nausea) and GTC
IV. Migrational Abnormalities
- Gray matter heterotopia
- Pachygyria/lissencephaly
- Focal cortical dysplasia
  - Transpial migration
  - Polymicrogyria
Overmigration: Cobblestone (Type II) Lissencephaly

Cobblestone lissencephaly (COBLIS)
- structural deficiency of basement membrane @ involved tissue (brain, muscle, retina)
- in brain = extraaxial migration of neurons

From Devisme Brain 2012

Adapted from:
Yatsenko Nat Comm 2014
Overmigration: Cobblestone (Type II) Lissencephaly

**Cobblestone lissencephaly (COBLIS)**
- structural deficiency of basement membrane @ involved tissue (brain, muscle, retina)
- in brain= extraaxial migration of neurons

**Dystroglycanopathies (COBLIS, A>P)**
- POMT1 (9q34)
- POMT2 (14q24)
- FKTN (9q31)
- FKRP (19q13)
- ISPD (7p21)
- LARGE (22q12)
- POMGnT1 (1p34)

**Laminopathies (COBLIS, P>A)**
- LAMA2 (6q22)
- LAMB1 (7q31)
- LAMC3 (9q34)

Guerrini *Lancet Neurol* 2014

Poor correspondence of dystroglycanopathy syndrome to mutation

Up to 1/3 of COBLIS wo genetic explanation

Adapted from: Yatsenko *Nat Comm* 2014
COBLIS Patient at 34 weeks GA & 10yo

Typical Type II Lissencephaly: Dysmyelination (A>P)

Lissencephaly with heterotopic islands of GM in subcortical WM

Kinked brainstem

Cystic cerebellar WM lesions

Occipital cephalocele

Eye abnormalities (PHPV)
Born at term at OSH with VP shunt for congenital hydrocephalus → transferred after developing ventriculitis

3T MRI @95 days old, 3T MRI: ISPD compound het

Better delineation of cobblestone lissencephaly

Cerebellar subcortical cysts

Vermian hypoplasia + kinked brainstem

Persistent hyperplastic primary vitreous (PHPV)
## Overmigration: Cobblestone (Type II) Lissencephaly

**Spectrum of phenotypes for dystroglycanopathies**

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<tbody>
<tr>
<td>Cortex ?</td>
<td>Frontal PMG and Temporo-occipital cobblestone cortex; small GM nodules</td>
<td>Frontal predominant cobblestone</td>
<td>Thick, cobblestone cortex with nonexistent sulci; small deep GM nodules</td>
</tr>
<tr>
<td>Myelination</td>
<td>Delayed and subcortical → deep WM</td>
<td>Delayed and subcortical → deep WM</td>
<td>Severe Hypo</td>
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<tr>
<td>Ventricles/Other*</td>
<td>Hydro less severe</td>
<td>May be present</td>
<td>Marked Hydrocephalus</td>
</tr>
<tr>
<td>Corpus Callosum*</td>
<td>Usu normal</td>
<td>May be hypoplastic</td>
<td>Hypoplasia</td>
</tr>
<tr>
<td>Brainstem*</td>
<td>Flat pons, Z-shaped kinking; fused colliculi</td>
<td>Flat pons, vertical midline cleft; fused large colliculi</td>
<td>Dorsal kink, hypoplastic pons with large fused colliculi + ventral cervicomedullary kink = Zig-zag shape</td>
</tr>
<tr>
<td>Cerebellum*</td>
<td>Dysmorphic folia with subcortical cysts; Vermis hypoplastic; No cephalocele</td>
<td>Dysmorphic folia with subcortical cysts; Vermis hypoplastic; No cephalocele</td>
<td>Small, dysmorphic cerebellum; vermian hypoplasia; 10% cephalocele</td>
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<tr>
<td>Eyes*</td>
<td>Mild (retinal dysplasias)</td>
<td>Colobomas, microphthalmia</td>
<td>Microphthalmos, glaucoma, retinal dysplasia, PHPV</td>
</tr>
<tr>
<td>Muscle</td>
<td>Hypotonia</td>
<td>Hypotonia</td>
<td>Profound Hypotonia</td>
</tr>
</tbody>
</table>
Overmigration: Cobblestone (Type II) Lissencephaly

**Spectrum of phenotypes for dystroglycanopathies**

CMD 1: “No” cortical malformation
- merosin/Lamininα2 (+): normal or mild cerebellar hypoplasia, WM abnl
- merosin/Lamininα2 (-): dys- or hypomyelination, central> subcortical WM
  4% with MCD

4F partially merosin deficient CMD

Limb girdle muscular dystrophy: **no CNS involvement**
IV. Migrational Abnormalities
- Gray matter heterotopia
- Pachygyria/lissencephaly
- Focal cortical dysplasia
  - Transpial migration
  - Polymicrogyria
Polymicrogyria (PMG): radio-pathologic enigma

Neuropathological criteria unsettled and surprisingly scarce
-e.g. fused molecular layer (I) w/ “festooning” of surface regardless of cortical layers (transpial separate)
-e.g. abnormal folding of one or more cortical layers regardless of fusion, lamination, or transpial neurons

Judkins *J Neuropathol Exp Neurol* 2011
Squier *Acta Neuropath Comm* 2014

Neuroradiological criteria straightforward but limited by spatial resolution
-increased *gyral frequency* (bumpy)
-nonanatomic sulci or distortion of sulci (e.g. central sulcus, sylvian fissure) in affected area
-apparent *thickening of cortex* (especially post myelination)
-sharp *gray-white matter interface* (where individual microgyri resolved)
-can be difficult to separate *transpial migration* from ordinary PMG
-Coarse, delicate (thin), sawtooth?  

Barkovich *Epilepsia* 2010
Polymicrogyria (PMG): radio-pathologic enigma

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- Coarse, delicate (thin), sawtooth?

Barkovich Epilepsia 2010
Polymicrogyria (PMG): Patterns

Distribution of PMG falls into several recognizable categories:

- **Perisylvian**
  - asymmetrical: 61%
  - unilateral: 5%
  - bilateral: 9%

- **Diffuse**
  - abnormal WM signal: 13%
  - unilateral: 8%

- **PVNH + PMG**: 11%

- **Frontal**
  - frontoparietal: 5%

- **Parasagittal parieto-occipital**: 3%

- **Other**: Multifocal, Sturge-Weber, Contra SCZ, Cleft/Transmantle

See: Leventer Brain 2010
Barkovich Epilepsia 2010

23M bilateral Rb/perisylvian PMG
3M right sided seizure: asymm Perisylvian PMG +
10M seizures, microcephaly Perisylvian PMG +
**Polymicrogyria (PMG): Patterns**

Distribution of PMG falls into several recognizable categories:

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Percentage</th>
<th>References</th>
</tr>
</thead>
<tbody>
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<td>Perisylvian</td>
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<td></td>
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<tr>
<td>- frontoparietal</td>
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<td></td>
</tr>
<tr>
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<td>3%</td>
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<tr>
<td>Other: Multifocal, Sturge-Weber, Contra SCZ, Cleft/Transmantle</td>
<td></td>
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</tr>
</tbody>
</table>

13F with **congenital CMV**: diffuse PMG

3mo with focal seizures
**Frontal PMG**
Polymicrogyria (PMG): Patterns

Distribution of PMG falls into several recognizable categories:

- **Perisylvian**
  - asymmetrical: 61%
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  - frontoparietal: 11%
  - frontoparietal: 1%

- **Parasagittal parieto-occipital**
  - Multifocal, Sturge-Weber, Contra SCZ, Cleft/Transmantle: 3%

**Other**

See: Leventer *Brain* 2010
Barkovich *Epilepsia* 2010

17M seizure: transmantle/PVNH, PMG

6F SOD, right SCZ and left PMG
Polymicrogyria (PMG): Patterns
Distribution of PMG falls into several recognizable categories:

**Perisylvian**
- asymmetrical 61%
- unilateral 5%

**Diffuse**
- abnormal WM signal 13%

**PVNH + PMG**
11%

**Frontal**
- frontoparietal 1%

**Parasagittal parieto-occipital**
3%

**Other:** Multifocal, Sturge-Weber, Contra SCZ, Cleft/Transmantle

See: Leventer *Brain* 2010
      Barkovich *Epilepsia* 2010
PMG: Versus Stenogyria

Stenogyria (polygyria): appearance of too many and compressed gyri
- does not correspond to underlying malformation at histology
- Unlike PMG
  - Uniform thickness (no nodularity)
  - Areas of polygyria do not survive scrutiny in multiple planes

Rorke-Adams Pathology of Chiari I and II Malformations in *The Chiari Malformations* (2013)
PMG: Etiologies

Large number of genetic and environmental causes: see Guerrini Lancet Neuro 2014

Environmental: microcephaly + calcification
   CMV (common):
   Ischemic (rare)

13F with congenital CMV: diffuse PMG
   -cerebellar hypoplasia
   -parenchymal calcification

2mo with congenital CMV infection
   -microcephaly
   -temporal lobe cysts
PMG: Etiologies

Large number of genetic and environmental causes: see Guerrini Lancet Neuro 2014

**Megalencephalic PMG**: overgrowth, polydactyly/syndactyly

- Megencephaly Capillary Malformation –Polymicrogyria (MCAP) Syndrome (PIK3CA, 3q26)
- Megalencephaly PMG Polydactyly Hydrocephalus (MPPH) Syndrome (PIK3R2, 19p13; AKT3, 1q43; CCND2, 12p13)

3F megalencephaly, right sided overgrowth, syndactyly, facial capillary malformation
- MCAP (PIK3CA mutation)
PMG: Etiologies

Large number of genetic and environmental causes: see Guerrini *Lancet Neuro* 2014

**Tubulinopathies**: callosal dysgenesis, cerebellar hypoplasia, basal ganglia cleavage abnormal
- DYNC1H1 (14q32), KIF5C (2q23), **TUBA1A** (12q13), TUBA8 (22q11), **TUBB2B** (6p25)*, TUBB3 (16q24)
  * Known to occur asymmetrically

4mo with **TUBA1A** PMG

3M with **TUBB2B** PMG(L) ?
PMG: Etiologies

Large number of genetic and environmental causes: see Guerrini *Lancet Neuro* 2014

**Skeletal Dysplasia**: Thanatophoric dysplasia with temporo-occipital lobe dysplasia (FGFR3, 4p16)

**CNVs** (e.g. 1p36, 22q11) predominantly perisylvian

**Misc. Syndromes**: CHARGE (CHD7, 8q12), Band-like Calcification + BFP PMG (OCLN, 5q13), Sturge-Weber

---

25wk GA **Thanatophoric Dysplasia** (FGFR3)

5do w/ TOF, hypocalcemia, clubfoot: **22q11**
Polymicrogyria vs. Cobblestone Lissencephaly

Cases of morphologic “polymicrogyria” may have neuronal subarachnoid infiltration like cobblestone lissencephalies
-”polymicrogyria-like”
-includes GPR56 and TUBB2B forms of genetically defined PMG(L)

27 week TUBB2B fetus

35 week GPR56 fetus

Bahl-Buisson *Brain* 2010
Jaglin *Nat. Genetics* 2009
V. Global Abnormalities in Size (Proliferation)
Embryology

Ventricular/Subventricular Zones

Neuronal Precursor Generation
(6-16 weeks)

Neuronal Migration
Ventricle $\rightarrow$ Cortex
(8-24 weeks)

Distinct processes but not completely separable
Microcephaly

Usually defined as <2-3 SD below the mean HC
Excluding insult/injury and errors of small molecule metabolism:
Congenital Microcephaly (apparent at birth)

Mitotic Spindle (Centrosome/Centriole): e.g. MCPH1, WDR62 (MCPH2), NDE1
Tubulin structure: TUBA1A, TUBB2B, kinesins
DNA repair genes: microcephalic primordial dwarf. (ATR), Nijmegen breakage syndrome

Postnatal Microcephaly (inadequate growth)
-e.g. Rett (MeCP2), Angelman (UBE3A), Rubinstein-Taybi (CBP/p300), CASK, FOXG1

Imaging: small head, simplified gyral pattern to varying degrees

5yo choreoathetoid CP, DD
Z=-13 @ 30 mo
17p12 VUS
“microcephaly vera”

18moF seizure, DD
HC 40.5cm @ 20 mo
DIAPH1 homozygous
Mild WM disease

1mo with microcephaly
Severe simplification, cortex nl
Microcephaly

Usually defined as <2-3 SD below the mean HC
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**Congenital Microcephaly (apparent at birth)**
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**Postnatal Microcephaly (inadequate growth)**
- e.g. Rett (MeCP2), Angelman (UBE3A), Rubinstein-Taybi (CBP/p300), CASK, FOXG1

**Imaging:** some forms associated with recognizable cortical malformation

---

Newborn **TUBA1A**
- microlissencephaly

**WDR62 mutants**
- microlissencephaly and PMG

From Bilguvar *Nature* 2010
Megalencephaly

Megalencephaly: weight > 2 SD above the mean

Excluding metabolic causes (e.g. megalenceph. leukoencephalopathy w/ cysts):

Rarely cortical malformation*: PTEN hamartoma sx (Cowden, Bananyan-Riley-Ruvalcaba),
RASopathies (Noonans, Costello, Legius, NF1), Basal cell nevus (PTCH1),
TBC1D7 (TSC1/2 interacting protein), STRADα/Lyk5

* That we know of

3M w/ Costello Syndrome
HC 56cm z=+4.6
Chiari I

8M macrocephaly & DD
Bananyan-Riley-Ruvalcaba, 10q23 deletion
HC 59.5cm
Cavernoma
Megalencephaly
Megalencephaly: weight > 2 SD above the mean

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**MCAP/MPPH PMG:** PIK3CA, PIK3R2, AKT3, CCND2

---

3F megalencephaly, right sided overgrowth, syndactyly, facial capillary malformation -MCAP (PIK3CA mutation) 

5mo progressive macrocephaly (HC z=11.97), DD, macrosmia, facial hemangiomas, polydactyly -not genetically characterized yet
Megalencephaly

Megalencephaly: weight > 2 SD above the mean
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- MCAP/MPPH PMG: PIK3CA, PIK3R2, AKT3, CCND2
- Hemimegalencephaly (HME): PIK3CA, PTEN, (AKT1), AKT3, TSC2, mTOR, DEPDC5

- overgrowth of a focal area, hemisphere, or whole brain
- cortical disorganization: features of FCDII, PMG, LIS, COBLIS, GM heterotopia

5moF with intractable seizure
1mo M intractable seizure
**Megalencephaly**

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Excluding metabolic causes (e.g. megalenceph. leukoencephalopathy w/ cysts):

- Rarely cortical malformation*: PTEN hamartoma sx (Cowden, Bananyan-Riley-Ruvalcaba), RASopathies (Noonans, Costello, Legius, NF1), Basal cell nevus (PTCH1)
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---

4F with scalp mass + ipsilateral cerebellar overgrowth
-no genetic data yet

2mo M with right hemihypertrophy & clinical CLOVES
-no genetic data yet

See Mirzaa & Poduri AJMG-C 2014
D’ Gama Ann. Neurol 2015
Hevner Sem. Perinatol 2014
**Megalencephaly**

Megalencephaly: weight > 2 SD above the mean

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  - overgrowth of a focal area, hemisphere, or whole brain
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---

6mo with intractable seizures with hypsarrhythmia R>L, R hemihypetrophy (verrucous plaques R hemibody)
- epidermal (linear sebaceous) nevus syndrome: no affected tissue genetics yet but usu somatic RASopathy
Megalencephaly

Megalencephaly: weight > 2 SD above the mean
Excluding metabolic causes (e.g. megalencephalopathy w/ cysts):

- Rarely cortical malformation*: PTEN hamartoma sx (Cowden, Bananyan-Riley-Ruvalcaba), RASopathies (Noonans, Costello, Legius, NF1), Basal cell nevus (PTCH1)
- MCAP/MPPH PMG: PIK3CA, PIK3R2, AKT3, CCND2
- Hemimegalencephaly (HME): PIK3CA, PIK3CR2, AKT1, AKT3, TSC2. mTOR, DEPDC5

- overgrowth of a focal area, hemisphere, or whole brain
- cortical disorganization: features of FCDII, PMG, LIS, COBLIS, GM heterotopia
Judging head size: don’t be fooled

Intraventricular cysts @ birth, 2 months
Judging head size: don’t be fooled

Intraventricular cysts @ birth, 2 months
VI. Fetal Life and Myelination Considerations
Embryology

- **Closed Neural Tube** (4 weeks)
- **Hemispheric Cleavage** (4-6 weeks)
- **Neuronal Precursor Generation** (6-16 weeks)
- **Ventricular/Subventricular Zones**
- **Corpus Callosum**
- **Neuronal Migration** (8-24 weeks)
- **Callosum Formation** Genu → Splenium (11-20 weeks)
Embryology

From ten Donkelaar
*Clinical Neuroembryology* 2010
Limitations by Gestational Age

- 20 weeks GA suspected HPE
- 24 weeks GA suspected ACC
Limitations by Gestational Age

- **21 weeks GA for VM**
- **19 weeks GA cleft palate**
- **20 weeks GA absent septum?**
- **21 weeks GA VM**

*Images show MRI scans at different gestational ages.*
Limitations by Gestational Age

36 week GA: SBH (DCX Female)

Newborn MR: PMG

2mo hypotelorism + CP: Lobar HPE

3mo ventriculitis: COBLIS
Limitations by Gestational Age

20 weeks GA absent septum?

21 weeks GA VM
Limitations by Gestational Age

20 weeks GA absent septum?

36 week GA: SBH (DCX Female)

21 weeks GA VM

3mo ventriculitis: COBLIS
Myelination & Brain Malformations

Myelination changes appearance of the abnormalities, sometimes greatly
“Negative” or discordant infant MR → repeat imaging >2 yo

1 yo w/ seizures

3 mo w/ seizures
Myelination & Brain Malformations

Myelination changes appearance of the abnormalities, sometimes greatly
“Negative” or discordant infant MR → repeat imaging >2 yo

1 yo w/ seizures

3 mo w/ seizures

9 years later …

15 mo later…

Extensive polymicrogyria

Subcortical and Transmantle GM Heterotopia
Myelination & Brain Malformations

Myelination changes appearance of the abnormalities, sometimes greatly “Negative” or discordant infant MR → repeat imaging at maturity (>2 yo).

Seizure @ 11 days

9 months

16 months

ILAE Iia at resection
Myelination & Brain Malformations

Myelination changes appearance of the abnormalities, sometimes greatly “Negative” or discordant infant MR → repeat imaging at maturity (>2 yo).

Microcephaly and seizures: 0 DOL and 10 yo

Polymicrogyria, possible intrauterine CMV exposure
Myelination & Brain Malformations

Myelination changes appearance of the abnormalities, sometimes greatly “Negative” or discordant infant MR → repeat imaging at maturity (>2 yo).
Asymmetric Myelination

One of the few causes of asymmetric myelination:

- Sturge Weber
- Malformation of Cortical Development
  - Focal Cortical Dysplasia
  - Hemimegalencephaly
  - Cobblestone lissencephaly

2 mo with new onset seizure
Overview

I. Schematic overview of brain development

II. Abnormalities of hemispheric cleavage

III. Commissural (Callosal) abnormalities

IV. Migrational abnormalities
   - Gray matter heterotopia
   - Pachygyria/Lissencephaly
   - Focal cortical dysplasia
   - Polymicrogyria
   - Transspial migration

V. Global abnormalities in size (proliferation)

VI. Fetal Diagnosis
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V. Michelle Silvera

Department of Radiology, CHOP
Arastoo Vossough, MD
Hisham Dahmoush, MBBCh FRCR

Email: edward.yang@childrens.harvard.edu
Question 1:
Lissencephaly is characterized as a failure in neuronal migration. Which of the following genes has NOT been implicated as causal for lissencephaly?

A) LIS1  
B) TUBA1A  
C) DCX (doublecortin)  
D) ARX  
E) TSC2 (tuberin)
Lissencephaly is characterized as a failure in neuronal migration. Which of the following genes has NOT been implicated as causal for lissencephaly?

A) LIS1
B) TUBA1A
C) DCX (doublecortin)
D) ARX
E) TSC2 (tuberin)

Answer is E.

The image depicts lissencephaly, in this instance due to the Miller-Dieker syndrome. Lissencephaly results from abnormal migration of neurons to the cortex such that a normal six layer cortex fails to form and a thick zone of arrested gray matter widens the cortex.

Option A is not correct. As the name suggests, Lis1 was the earliest characterized lissencephaly gene.
Option B is not correct. Tubulin mutations represent a small proportion of lissencephaly cases but are well accepted genetic etiology for this disorder.
Option C is not correct. DCX mutations are the most common reason for X-linked lissencephaly.
Option D is not correct. ARX mutations are a rare but well accepted cause of lissencephaly, usually presenting as ambiguous genitalia and callosal dysgenesis in males.
Option E is correct. TSC1 and TSC2 cause tuberous sclerosis. The tubers in tuberous sclerosis represent a form of cortical dysplasia, and while other malformations (namely hemimegalencephaly) have been linked to TSC1/2, lissencephaly is not one of them.

References:
Question 2:
A 13 year old female with spastic quadraparesis is imaged with the MRI shown below. Which of the following is the MOST likely explanation for the brain malformation?

A) Megalencephaly Capillary Malformation Polymicrogyria (MCAP) syndrome
B) Somatic mutation in AKT1
C) Congenital cytomegalovirus (CMV) exposure.
D) Filamin A mutation (FLNA)
E) Trisomy 13
Question 2:
A 13 year old female with spastic quadraparesis is imaged with the MRI shown below. Which of the following is the MOST likely explanation for the brain malformation?

A) Megalencephaly Capillary Malformation Polymicrogyria (MCAP) syndrome
B) Somatic mutation in AKT1
C) Congenital cytomegalovirus (CMV) exposure.
D) Filamin A mutation (FLNA)
E) Trisomy 13

Answer is C.

This case features marked microcephaly with diffuse polymicrogyria, callosal dysgenesis, cerebellar hypoplasia, and parenchymal calcifications. These findings are typical of congenital CMV exposure.

Option A is not correct. MCAP syndrome is associated with polymicrogyria but as the name suggests, there is enlarged head size unlike the shown image.
Option B is not correct. In the brain, somatic mutations of AKT1 result in hemimegalencephaly. In the shown case, the abnormality is diffuse and results in small head size.
Option C is correct. CMV exposure in utero results in small head size, polymicrogyria, parenchymal calcifications, and cerebellar hypoplasia. All these features are present in the shown case.
Option D is not correct. In the brain, FLNA mutations are associated with periventricular nodular heterotopia rather than polymicrogyria. The microcephaly and parenchymal calcifications are also discordant features.
Option E is not correct. Trisomy 13 is most associated with holoprosencephaly rather than polymicrogyria.

References:
Question 3:
This case was shown earlier. What embryologic process has failed to occur normally?

A) Hemispheric cleavage
B) Neuronal precursor proliferation
C) Neuronal migration
D) Commissuration
E) Fenestration of the posterior membranous area
Question 3:
This case was shown earlier. What embryologic process has failed to occur normally?

A) Hemispheric cleavage
B) Neuronal precursor proliferation
C) Neuronal migration
D) Commissuration
E) Fenestration of the posterior membranous area

Answer is A.

The panel of images demonstrate continuity of the cerebral hemispheres across the midline with vertically oriented sylvian fissures and an absent septum pellucidum. The genu and splenium of the corpus callosum are present but the midportion of the callosum is unidentifiable. This case was shown earlier and represents the middle interhemispheric variant of holoprosencephaly.

Option A is correct. Holoprosencephaly represents failure of the brain to cleave into two separated hemispheres.

Option B is not correct. Neuronal precursor proliferation occurs after hemispheric cleavage has already occurred. Failures in this step result in smaller overall size of the brain.

Option C is not correct. This step also occurs after hemispheric cleavage and leads to malformations such as gray matter heterotopia, pachygyria, polymicrogyria, and focal cortical dysplasia.

Option D is not correct. While the corpus callosum is not normal in this case, the reason for the abnormal configuration is failure of the hemispheres to separate, not failure of the commissures to form in the first place.

Option E is not correct. Fenestration of the posterior membranous area is an early step in formation of the brain, but it is tied to formation of the outlet foramina of the fourth ventricle. Failures in this process result in Dandy Walker spectrum abnormalities not holoprosencephaly.

References: