Pediatric Neuropathology: Malformations

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I have no relevant financial relationships to disclose
Learning Objectives

• Describe the basic steps of cortical development and how disruptions in each step may result in different types of cortical malformations.

• Compare and contrast the gross findings, microscopic features and etiologies of lissencephaly type I (classic) and lissencephaly type II (cobblestone).

• List the most common genetic and non-genetic etiologies associated with holoprosencephaly.

• Cite an example of how mutations in one gene may result in different phenotypes/malformations.
Outline

• Disorders of forebrain induction
  – Alobar holoprosencephaly
  – Semilobar holoprosencephaly
  – Lobar holoprosencephaly
  – Agenesis of the corpus callosum

• Malformations of cortical development
  – Lissencephaly
  – Heterotopias
  – Cortical dysplasia with cytomegaly
    • Focal cortical dysplasia
    • Tuberous Sclerosis

• Virtual Slides
Malformations

- Genetic and environmental factors have been implicated in the etiology of CNS malformations

- Most birth defects are likely multifactorial (combination of genetic, epigenetic and environmental)
Disorders of Forebrain Induction

- Alobar holoprosencephaly
- Semilobar holoprosencephaly
- Lobar holoprosencephaly
- Agenesis of the corpus callosum
Holoprosencephaly

- Developmental defect of the forebrain (prosencephalon)
- Incomplete separation of the cerebral hemispheres into distinct right and left halves
- Mostly sporadic (occasional familial cases)
- Prevalence:
  - 1:16,000 live births
  - 1:250 conceptuses
- Three types:
  - Alobar (complete): no separation of the telencephalon, single ventricle in a small brain
  - Semilobar (incomplete): variable degrees of separation of the posterior cerebrum
  - Lobar: a small focal fusion of the midline with T-shaped or Y-shaped lateral and third ventricles
Alobar Holoprosencephaly
Alobar Holoprosencephaly

Figures 2.7-3 and 2.7-5, Pediatric Neuropathology: A Text-Atlas
Semilobar Holoprosencephaly
Lobar Holoprosencephaly
Holoprosencephaly Clinical Features

- Cleft lip/palate
- Eye anomalies (cyclopia)
- Anosmia
- Congenital nasal pyriform aperture stenosis
- Single central maxillary incisor
- Pituitary dysfunction (including SIADH)
- Seizures
- Hypotonia
Holoprosencephaly Etiology

- Material diabetes mellitus
- Infections: toxoplasmosis, syphilis, rubella
- Teratogens: ethanol, retinoic acid, cholesterol synthesis inhibitors
- Genetic factors:
  - Cytogenetic abnormalities seen in 50% of cases
    - Trisomy 13 most frequent
  - Smith-Lemli-Opitz syndrome (*DHCR7*)
  - Mutations (see next slide)
<table>
<thead>
<tr>
<th>Disease or locus name</th>
<th>CNS malformations involved</th>
<th>Gene</th>
<th>Function of gene product</th>
<th>Chromosome location</th>
<th>OMIM number</th>
<th>Mouse model or homologue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holoprosencephaly (HPE1)</td>
<td>Alobar holoprosencephaly</td>
<td>ND</td>
<td>ND</td>
<td>21q22.3</td>
<td>236100</td>
<td>ND</td>
</tr>
<tr>
<td>Holoprosencephaly (HPE2)</td>
<td>Alobar or semi-lobar holoprosencephaly</td>
<td>SOX3</td>
<td>Homologue of sine oculis gene of Drosophila: homeobox-containing transcription factor</td>
<td>2p21</td>
<td>157170</td>
<td>Targeted mutation of Six3 gene has truncation of forebrain</td>
</tr>
<tr>
<td>Holoprosencephaly (HPE3)</td>
<td>Holoprosencephaly</td>
<td>SHH (Sonic hedgehog)</td>
<td>Secreted signalling molecule; neural inducer</td>
<td>7q36</td>
<td>142945</td>
<td>Targeted mutation of Shh gene has holoprosencephaly in addition to many other defects</td>
</tr>
<tr>
<td>Holoprosencephaly (HPE4)</td>
<td>Holoprosencephaly</td>
<td>TGF-β</td>
<td>Homeodomain protein functioning as repressor of TGF-β</td>
<td>18p11.3</td>
<td>142346</td>
<td>Targeted mutation of Tgf-β gene produces no visible phenotype</td>
</tr>
<tr>
<td>Holoprosencephaly (HPE5; 13q32 deletion syndrome)</td>
<td>Holoprosencephaly, exencephaly</td>
<td>ZIC2</td>
<td>Transcription factor encoded by homologue of odd paired gene of Drosophila</td>
<td>13q32</td>
<td>609637</td>
<td>Targeted mutation of Zic2 gene has holoprosencephaly</td>
</tr>
<tr>
<td>Holoprosencephaly (HPE8)</td>
<td>Holoprosencephaly</td>
<td>ND</td>
<td>ND</td>
<td>2q37.1</td>
<td>605934</td>
<td>ND</td>
</tr>
<tr>
<td>Holoprosencephaly (HPE7)</td>
<td>Holoprosencephaly</td>
<td>PTCH1</td>
<td>Patched: membrane receptor for Sonic hedgehog protein</td>
<td>9q22.3</td>
<td>601309</td>
<td>Targeted mutation of Patch1 causes medulloblastoma in heterozygotes and neural tube defects in homozygotes</td>
</tr>
<tr>
<td>Holoprosencephaly (HPE8)</td>
<td>Holoprosencephaly</td>
<td>ND</td>
<td>ND</td>
<td>14q13</td>
<td>609406</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND = not determined
Agenesis of the Corpus Callosum

• Complete (total) and incomplete (partial) types
  – Partial is usually only missing the splenium

• Isolated (silent clinically or subtle) or seen in association with other malformations (ex. holoprosencephaly)

• May be sporadic but typically associated with syndromes: Aicardi, Andermann, Meckel

• Possible pathogenetic mechanisms:
  – Probst bundle of misdirected fibers
  – Mechanical defect suggested by hamartoma/ lipoma
Agenesis of the Corpus Callosum

Images courtesy of Brian Harding, DPhil FRCPath
Outline

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• Malformations of cortical development
  – Lissencephaly
  – Heterotopias
  – Cortical dysplasia with cytomegaly
    • Focal cortical dysplasia
    • Tuberous Sclerosis
Development of the Cerebral Cortex
## Malformations of cortical development with associated genes and clinical features

<table>
<thead>
<tr>
<th>Developmental stage</th>
<th>Cortical malformation</th>
<th>Genetic cause</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal neurogenesis</td>
<td>Microcephaly</td>
<td>ASPM</td>
<td>Mental retardation, not generally associated with epilepsy, autosomal recessive inheritance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Microcephalin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CDK5RAP2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CENP1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemimegalencephaly</td>
<td>Unknown</td>
<td>Mental retardation, early onset seizures (frequently intractable epilepsy), +/- neurocutaneous syndrome</td>
</tr>
<tr>
<td></td>
<td>Focal cortical dysplasia</td>
<td>Unknown</td>
<td>Most common, focal and generalized seizures</td>
</tr>
<tr>
<td>Abnormal neuronal migration</td>
<td>Periventricular heterotopia</td>
<td>FLNA</td>
<td>Normal intelligence, adolescent onset seizures, X-linked disorder with male lethality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ARFGEF2</td>
<td>Mental retardation, microcephaly, autosomal recessive inheritance, rare</td>
</tr>
<tr>
<td></td>
<td>Subcortical band heterotopia</td>
<td>DCX</td>
<td>Subcortical band heterotopia in females, mental retardation, epilepsy, X-linked disorder</td>
</tr>
<tr>
<td></td>
<td>Lissencephaly</td>
<td>LIS1</td>
<td>Miller-Dieker syndrome (characteristic facial features), autosomal dominant inheritance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DCX</td>
<td>Lissencephaly in males, X-linked</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TUBA1A</td>
<td>Lissencephaly, clinical features similar those caused by LIS1 and DCX, de novo mutations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ARX</td>
<td>Associated with ambiguous genitalia, hypothalamic dysfunction, neonatal epilepsy, X-linked disorder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RELN</td>
<td>Associated with cerebellar hypoplasia, epilepsy, autosomal recessive inheritance</td>
</tr>
<tr>
<td>Abnormal arrest in neuronal migration</td>
<td>Cobblestone lissencephaly</td>
<td>Fukutin</td>
<td>Fukuyama congenital muscular dystrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FOMGnT1</td>
<td>Muscle-eye-brain disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FOMT1</td>
<td>Walker-Warburg Syndrome</td>
</tr>
</tbody>
</table>

Lissencephaly type I (Classic)

- Neuronal migration disorder characterized by abnormal gyri
- Varies from agyria to pachygyria
- Severe mental retardation, hypotonia, intractable seizures
- Several genetic types are recognized
Lissencephaly type I
<table>
<thead>
<tr>
<th>Disease</th>
<th>CNS</th>
<th>Gene</th>
<th>Function of product</th>
<th>Chromosome</th>
<th>Mouse model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lissencephaly (type I): autosomal recessive (Norman-Roberts type)</td>
<td>Lissencephaly with low sloping forehead and prominent nasal bridge</td>
<td>RELN</td>
<td>Reelin: extracellular matrix protein produced by Cajal-Retzius cells required for neuronal migration</td>
<td>7q22</td>
<td>reeler mutant mouse causes cerebellar and cerebral cortical lamination anomalies</td>
</tr>
<tr>
<td>Lissencephaly (type I): Miller-Dieker syndrome, autosomal dominant (haploinsufficiency)</td>
<td>Lissencephaly, cerebral heterotopias, facial dysmorphism</td>
<td>LIS1 and 14-3-3ε</td>
<td>LIS1: Non-catalytic subunit of brain platelet-activating factor acetyl hydrolase (PAFAH)</td>
<td>17p13.3</td>
<td>Targeted loss of function alleles of Pafah1b1 gene and 14-3-3ε</td>
</tr>
<tr>
<td>Lissencephaly (type I): isolated lissencephaly sequence (ILS), autosomal dominant</td>
<td>Lissencephaly</td>
<td>LIS1 deletion alone</td>
<td>LIS1: as above</td>
<td>17p13.3</td>
<td>Targeted loss of function alleles of Pafah1b1 gene causes neuronal migration disorders</td>
</tr>
<tr>
<td>Lissencephaly (type I): X-linked</td>
<td>Lissencephaly with agenesis of corpus callosum in males; subcortical band heterotopia in females</td>
<td>DCX</td>
<td>Doublecortin: microtubule-associated protein that interacts with non-receptor tyrosine kinases, including Abl</td>
<td>Xq22.3-q23</td>
<td>suppression of doublecortin expression by RNAi inhibits neuronal migration in rat neocortex</td>
</tr>
<tr>
<td>Lissencephaly (type I): X-linked (XLAG)</td>
<td>Lissencephaly with ambiguous genitalia</td>
<td>ARX</td>
<td>Aristaless-related homeodomain transcription factor</td>
<td>Xp22.13</td>
<td>Targeted mutation of Arx</td>
</tr>
</tbody>
</table>
Layer
I
II
III
IV
V
VI
WM

Normal

LIS1

DCX

ARX

Mutations

4 layer cortex with posterior predominance
4 layer cortex with anterior predominance
3 layer cortex with posterior predominance

Adapted from Forman MS et al. J Neuropathol Exp Neurol 2005
Normal
Lissencephaly type I: Isolated Lissencephaly

- Isolated lissencephaly sequence occurs in patients with deletions of the \textit{LIS1} gene

- Autosomal dominant

- \textit{LIS1} encodes the non-catalytic subunit of platelet activating factor acetyl hydrolase
  - Involved in the regulatory pathway for dynein
  - Important for neuronal migration

- More severe occipital/posterior parietal
Lissencephaly type I: Miller-Dieker syndrome

- Clinical features:
  - Microcephaly, bitemporal narrowing, vertical ridging in forehead, micrognathia
  - Cryptorchidism, heart and kidney anomalies may be seen

- Due to codeletion of \textit{LIS1} and \textit{14-3-3} genes (both on the short arm of chromosome 17)

- Lissencephaly due to deletion of \textit{LIS1}

- Facial features due to other genes on 17p
Miller-Dieker syndrome

Images courtesy of Brian Harding, DPhil FRCPath
Lissencephaly type I: doublecortin (DCX) gene mutation

- Located on Xq22
- X-linked dominant
- In males, isolated lissencephaly
- More severe anteriorly
Lissencephaly type I: XLAG

- X-linked lissencephaly with ambiguous genitalia (XLAG)
  - Due to ARX mutations
  - X-linked recessive
  - Agenesis of the corpus callosum, severe seizures, temperature dysregulation, microcephaly
  - Posterior-anterior gradient
  - 3-layer cortex
XLAG

Images courtesy of Brian Harding, DPhil FRCPath
Lissencephaly Type II (Cobblestone)

• Autosomal recessive

• Cortex unlayered disorganized with cobblestone surface and thickened meninges

• Variable muscular and ocular involvement with CNS disorders
Lissencephaly Type II (Cobblestone)
<table>
<thead>
<tr>
<th>Disease</th>
<th>CNS</th>
<th>Gene</th>
<th>Function of product</th>
<th>Chromosome</th>
<th>Mouse model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lissencephaly (type II): Fukuyama congenital muscular dystrophy</td>
<td>Cobblestone lissencephaly, polymicrogyria</td>
<td>FCMD</td>
<td>Fukutin: gene interrupted by retro-transposon insertion. A secreted protein, which may function as a glycosyl transferase in the Golgi</td>
<td>9q31</td>
<td>Targeted mutation of FCMD gene causes muscular dystrophy and cortical dysplasia</td>
</tr>
<tr>
<td>Lissencephaly (type II): muscle-eye-brain disease, type A, 5; type B, 5; type C, 5</td>
<td>Cobblestone lissencephaly, congenital myopia, glaucoma, retinal hypoplasia, mental retardation, hydrocephalus</td>
<td>FKRP</td>
<td>Protein targeted to the medial Golgi apparatus and necessary for posttranslational modification of dystroglycan</td>
<td>19q13.3</td>
<td></td>
</tr>
<tr>
<td>Lissencephaly (type II): Walker-Warburg syndrome</td>
<td>Agyria, cobblestone lissencephaly, cerebellar dysplasia and vermal agenesis, hydrocephaly, occipital encephalocele</td>
<td>POMT1, POMT2</td>
<td>O-mannosyl transferase 1: first enzyme in synthetic pathway of O-mannosyl glycans</td>
<td>9q31-q33, 14q24.3</td>
<td>Large(myd) mutant and targeted mutation of α dystroglycan gene provide models of Walker-Warburg syndrome</td>
</tr>
<tr>
<td>Lissencephaly (type II): muscle-eye-brain disease</td>
<td>Cobblestone lissencephaly, congenital myopia, glaucoma, retinal hypoplasia, mental retardation, hydrocephalus</td>
<td>POMGnT1</td>
<td>O-mannose β-1,2-N-acetyl glucosaminyl transferase: second enzyme in synthetic pathway of O-mannosyl glycans</td>
<td>1p34-p33</td>
<td>Targeted mutation of POMGnT1 gene causes phenotype resembling muscle-eye-brain disease</td>
</tr>
<tr>
<td>Lissencephaly (type II): muscle-eye-brain disease</td>
<td>Cobblestone lissencephaly, congenital myopia, glaucoma, retinal hypoplasia, mental retardation, hydrocephalus</td>
<td>LARGE</td>
<td>Interacts directly with dystroglycan to allow glycosylation</td>
<td>22q12</td>
<td></td>
</tr>
</tbody>
</table>
Lissencephaly Type II

• Walker–Warburg syndrome
  – AKA HARD+E syndrome (hydrocephalus, agyria, retinal dysplasia, encephalocele) and cerebro-ocular dysplasia–muscular dystrophy syndrome
  – Cobblestone lissencephaly, cerebellar dysplasia and vermal agenesis, hydrocephaly, occipital encephalocele, congenital muscular dystrophy
  – Variety of ocular anomalies
  – Die in infancy
  – Associated with mutations in \textit{POMT1} and \textit{POMT2} genes

• Muscle-Eye-Brain disease
  – Generalized muscle weakness, contractures, seizures, eye anomalies, cobblestone lissencephaly
  – Associated with mutations in \textit{POMGnT1}, \textit{LARGE}, and \textit{FKRP}
Lissencephaly Type II: Walker–Warburg syndrome

Images courtesy of Brian Harding, DPhil FRCPath
LISSENCEPHALY TYPE II: WALKER–WARBURG SYNDROME

Images courtesy of Brian Harding, DPhil FRCPath
Gray Matter Heterotopia

- Clusters of neurons and glia that form a region of gray matter in an abnormal location
- May be single or multiple, line ventricles, in deep white matter, subcortical white matter, leptomeninges
- Overlying cortex can be normal or disrupted
- May have normal intelligence and normal neurologic exam
Nodular Heterotopia
NODULAR HETEROTOPIA
Nodular Heterotopias: Etiology

• Reported following fetal insults:
  – Sustained maternal hyperthermia
  – Methylmercury poisoning
  – Radiation

• Familial subependymal heterotopia usually found in females:
  – Consistent with X-linked dominant inheritance (lethal in males)
  – Strong correlation with epilepsy
  – Mutations in *Filamin 1 (FLNA)* on Xq28 → actin binding protein associated with cytoskeleton and is important for cell migration

• Periventricular nodular heterotopia with microcephaly
  – Mutation in *ARFGEF2*
  – Autosomal recessive
Band (Laminar) Heterotopia

- Bilateral bands of heterotopic gray matter in the white matter located between the lateral ventricular walls and the cortex
  - Overlying cortex may be normal or have simplified gyral pattern
  - Mild to moderate mental retardation
  - Seizures, often with later onset
Band Heterotopia

Images courtesy of Brian Harding, DPhil FRCPath
Band Heterotopia

• Rare, non-lethal
  – May cause epilepsy

• Predominantly in females

• DCX mutations detected in many patients
Cortical Dysplasia with Cytomegaly

- Focal cortical dysplasia
- Tuberous Sclerosis
# Focal Cortical Dysplasia

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I</strong></td>
<td>Isolated FCD</td>
</tr>
<tr>
<td>Ia</td>
<td>Abnormal radial cortical lamination</td>
</tr>
<tr>
<td>Ib</td>
<td>Abnormal horizontal cortical lamination</td>
</tr>
<tr>
<td>Ic</td>
<td>Abnormal radial and horizontal cortical lamination</td>
</tr>
<tr>
<td><strong>II</strong></td>
<td>Isolated FCD</td>
</tr>
<tr>
<td>IIa</td>
<td>Dysmorphic neurons</td>
</tr>
<tr>
<td>IIb</td>
<td>Dysmorphic neurons and balloon cells</td>
</tr>
<tr>
<td><strong>III</strong></td>
<td>Cortical lamination abnormalities associated with principal lesion</td>
</tr>
<tr>
<td>IIIa</td>
<td>FCD in the temporal lobe + hippocampal sclerosis</td>
</tr>
<tr>
<td>IIIb</td>
<td>FCD adjacent to a glial or glioneuronal tumor</td>
</tr>
<tr>
<td>IIIc</td>
<td>FCD adjacent to a vascular malformation</td>
</tr>
<tr>
<td>IIIId</td>
<td>FCD adjacent to an acquired lesion (ex. trauma, ischemic injury)</td>
</tr>
</tbody>
</table>
Focal Cortical Dysplasia
Focal Cortical Dysplasia, Type IIa
Focal Cortical Dysplasia, Type IIb
Tuberous Sclerosis
Tuberous Sclerosis

Images courtesy of Brian Harding, DPhil FRCPth; Figure 7.1-5, Pediatric Neuropathology: A Text-Atlas
Tuberous Sclerosis: etiology

- Locus heterogeneity with disease-determining genes:
  - TSC1 on chromosome 9 (protein = hamartin)
  - TSC2 on chromosome 16 (protein = tuberin)

- TSC1 and 2 gene products are strategically important in cell growth and turnover
  - Thought to be tumor suppressors
  - Mutations lead to hyperactivation of the mTOR signaling pathway

Virtual Slides

https://pathpresenter.net/#/public/display?token=bbc29011
Summary

• Disorders of forebrain induction
  – Alobar holoprosencephaly
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  – Lobar holoprosencephaly
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  – Cortical dysplasia with cytomegaly
    • Focal cortical dysplasia
    • Tuberous Sclerosis
Questions?
References