Genetics of CNS abnormalities
The prenatal Diagnosis Perspective

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General Principles

• Major anomalies can be seen as early as the first trimester: e.g. anencephaly, holoprosencephaly
• Many CNS defects are not detectable until past 20-22 weeks
• Limited and evolving phenotypes throughout pregnancy
• Associated abnormalities
• Functional sequelae cannot be assessed
• Multiple imaging modalities and timing (Ultrasound & MRI)
• Multidisciplinary approach
Multidisciplinary Approach for Diagnosis and Management

- Prenatal care provider
- Sonographer
- Maternal-fetal medicine
- Radiology
- Prenatal and pediatric genetics
- Neonatology
- Pediatric neurology
- Neurosurgery
- Other subspecialties (associated defects)
- Perinatal Hospice (PPACT: Perinatal Pediatric Advanced Care Team)
Importance of a Prenatal Genetic Evaluation

• Syndromic vs. non-syndromic
• Prognosis counseling – reducing uncertainty
• Preparation of families
• Recurrence risk counseling
• Prenatal and perinatal management decisions
• Treatments that improve outcomes, life quality, developmental potential exist for some disorders

• Limited time to get genetic diagnosis
• Important decisions are made
Amniocentesis should be offered when there are birth defects

- Cells are of fetal origin: genetic testing
- **RISKS:** older data 1 in 300-500
- New meta analysis: ~1/909
- ACOG revised: 0.1-0.3%
- Chromosomal microarray
- (Karyotype)
- (Single gene testing)
- Panel or **exome**
# Chromosomal abnormalities in CNS defects (complex phenotypes)

<table>
<thead>
<tr>
<th>CNS anomaly</th>
<th>% abnl</th>
<th>Predominant karyotypic abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcephaly</td>
<td>frequent</td>
<td>T9, T13, T18, SCA</td>
</tr>
<tr>
<td>Holoprosencephaly</td>
<td>50</td>
<td>T13, T18</td>
</tr>
<tr>
<td>Dandy-Walker malformation</td>
<td>45-55</td>
<td>T9, T13, T18, T21, triploidy, del3q24, del6p25, dup5p, dup8p, dup8q</td>
</tr>
<tr>
<td>Micro-anophthalmia</td>
<td>25+</td>
<td>T13</td>
</tr>
<tr>
<td>Agenesis of corpus callosum</td>
<td>18</td>
<td>T8, T13, T18, del11q</td>
</tr>
<tr>
<td>Spina bifida meningomyelocele</td>
<td>17</td>
<td>T13, T18, triploidy</td>
</tr>
<tr>
<td>Isolated ventriculomegaly</td>
<td>12</td>
<td>T21, 47,XXY</td>
</tr>
<tr>
<td>Anencephaly</td>
<td>9</td>
<td>Variable, incl T13, T18, triploidy</td>
</tr>
<tr>
<td>Chiari malformation</td>
<td>occasional</td>
<td>T13, T18</td>
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</tbody>
</table>

Microarray Utility for prenatally detected Fetal Structural Congenital anomalies

(Hillman, 2013)
Value of prenatal CMA in fetuses with structural abnormalities and normal karyotype varies by type of anomaly

<table>
<thead>
<tr>
<th>Anomaly type</th>
<th>Pooled prevalence (95% CI)</th>
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<tbody>
<tr>
<td>Cardiac</td>
<td>22/476 = 4.6% (2.7-6.5)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>5/81 = 6.2% (0.9-11.4)</td>
</tr>
<tr>
<td>CNS</td>
<td>35/563 = 6.2% (4.2-8.2)</td>
</tr>
<tr>
<td>Facial</td>
<td>6/113 = 5.3% (1.2-9.4)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>24/305 = 7.9% (4.8-10.9)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>7/105 = 6.7% (1.9-11.4)</td>
</tr>
<tr>
<td>Urogenital</td>
<td>9/153 = 5.9% (2.2-9.6)</td>
</tr>
<tr>
<td>Increased NT &gt; 3.5 mm</td>
<td>5/162 = 3.1% (0.4-5.7)</td>
</tr>
<tr>
<td>Cystic Hygroma</td>
<td>12/262 = 4.6% (2.0-7.1)</td>
</tr>
<tr>
<td>Total isolated anomalies</td>
<td>125/2220 = 5.6% (4.7-6.6)</td>
</tr>
<tr>
<td>Multiple anomalies</td>
<td>104/1139 = 9.1% (7.5-10.8)</td>
</tr>
<tr>
<td>All anomalies</td>
<td>229/3359 = 6.8% (6.0-7.7)</td>
</tr>
</tbody>
</table>
## Copy Number Changes

<table>
<thead>
<tr>
<th>System or Malformation</th>
<th>isolated</th>
<th>With anomaly in other systems</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Significant finding</td>
<td>DR %</td>
<td>Significant finding</td>
</tr>
<tr>
<td>Total CNS</td>
<td>25/382</td>
<td>6.5</td>
<td>35/317</td>
</tr>
<tr>
<td>Posterior fossa defects</td>
<td>5/74</td>
<td>6.8</td>
<td>16/70</td>
</tr>
<tr>
<td>Cerebellar Hypoplasia</td>
<td>5/30</td>
<td>16.7</td>
<td>5/21</td>
</tr>
<tr>
<td>Dandy Walker Malformation</td>
<td>1/44</td>
<td>2.3</td>
<td>11/43</td>
</tr>
<tr>
<td>Holoprosencephaly</td>
<td>8/53</td>
<td>15.1</td>
<td>1/32</td>
</tr>
<tr>
<td>Ventriculomegaly</td>
<td>3/84</td>
<td>3.6</td>
<td>10/88</td>
</tr>
<tr>
<td>Agenesis of Corpus Callosum</td>
<td>2/45</td>
<td>4.4</td>
<td>2/24</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>1/32</td>
<td>3.1</td>
<td>1/5</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>3/66</td>
<td>4.5</td>
<td>2/34</td>
</tr>
<tr>
<td>Spinal Defects</td>
<td>0/20</td>
<td>0.0</td>
<td>2/35</td>
</tr>
</tbody>
</table>

Exome Sequencing has Accelerated Gene Discovery in Developmental Brain Disorders

![Graph showing the increase in known genetic associations from 2005 to 2014.]

- 27 known genetic associations in 2005
- >100 known genetic associations in 2012
- ~200 known genetic associations in 2014

**Figure 1.** The past decade has seen a rapid rate of gene discovery in developmental brain disorders.

**Contribution of exome sequencing**

- Single gene disorders

**High diagnostic rate for CNS defects in recent prenatal and early neonatal exome studies**

- BCM ~35%

Agenesis and Dysgenesis of Corpus Callosum (ACC)

- CC not developed until 18-20 weeks, continues to thicken until after birth
  - Early signs: absent cavum septum pellucidum, colpocephaly
  - US has 20% FPR - If suspected, consider MRI (22 weeks)
- One of the most common CNS abnormalities diagnosed in the fetus: complete or partial
- Prevalence of ACC:
  - ~1:1000 overall but 2-3% if intellectual disability
  - ~50% have other CNS abnormalities,
  - Up to 65% have non-CNS abnormalities
  - 5-20% isolated ACC prenatally → associated anomalies postnatally

ACC at 28w3d

Agenesis and Dysgenesis of Corpus Callosum (ACC)

- **Etiological heterogeneity:**
  - Chromosomal abnormality: 17.8%
  - If normal karyotype: CNV in 5.8% - 9.4%
  - Syndromic: many syndromes in OMIM have ACC
  - Single genes in isolated ACC
  - Metabolic / Environmental / rarely vascular, hypoxic

- **Prognosis:**
  - Syndromic: depends on associated syndrome
  - Isolated:
    - 70-80% have normal intelligence
    - 20-30% have neurodevelopmental delay, of which 11% severe in some series
    - All may be predisposed to learning and social deficits

ACC at 28w3d

Some syndromes with ACC

- Aicardi syndrome: no gene known
- Mowat-Wilson syndrome: ZEB2
- Acrocallosal syndrome: KIF7
- ATR-X disorders: ATRX
- Opitz G syndrome: MID1
- Mental retardation Adducted thumbs, Shuffling gait, Ataxia (MASA) and hydrocephalus with aqueductal stenosis: L1CAM

Hydrocephalus

• Incidence:
  – ~1:1000 live births
  – *Mild* ventriculomegaly (VM) (10-12 mm): 10% - 40% (?) associated abnormalities
  – *Moderate* VM (12.1-15 mm): up to 76% (?) associated abnormalities
  – *Severe* VM (>15 mm): 60% associated abnormalities (ACC, NTD)

• Multifactorial:
  • Primary
  • Secondary:
    – Environmental (infection)
    – Obstructive – non-obstructive


*D’Addario V, Rossi AC. Semin Fetal Neonat Med 2012;17:310-318*
Hydrocephalus

• Prognosis:
  – Primary: depends on genetic mutation / disorder and associated abnormalities
    • more associated anomalies if symmetrical VM; 39% vs. 24%
  – Secondary: depends on cause
  – Injury to the brain from mass effect and pressure
  – Severe: 11-62.5% no neurological deficit
  – Mild: 77.4%-100% no neurological deficit
  – But limited studies on long-term outcome

D’Addario V, Rossi AC. Semin Fetal Neonat Med 2012;17:310-318
Genetic defects and Hydrocephalus

• Chromosomal abnormalities:
  – Mild VM: 2-3%;
  – Moderate VM: 14.2%;
  – Severe VM: 17.4%
  – With associated abnormalities: >15%
  – If normal karyotype: clinically significant CNVs in 7.6%

• Associated with other defects - syndromes

Aqueductal stenosis at 21w2d


D’Addario V, Rossi AC. Semin Fetal Neonat Med 2012;17:310-318
X-linked aqueductal stenosis

- **L1CAM** gene in Xq28
- Males + severe hydrocephalus (+ aqueductal stenosis) → 57/138 (41%) have mutations in *L1CAM*
- Adducted thumbs in 88%
- Aqueductal stenosis in 90%
- Pyramidal tract hypoplasia (role for prenatal tractography?)
- Agenesis of corpus callosum in 68%
- MASA: mental retardation, adducted thumbs, shuffling gait, aphasia

D’Addario V, Rossi AC. Semin Fetal Neonat Med 2012;17:310-318
Holoprosencephaly (HPE)

- 1:250 conceptuses
- 0.4-1.2:10,000 live births
  - Most affected fetuses do not survive
- 40% Alobar, 43% semilobar, 17% lobar
- Variants: interhemispheric and septo-preoptic
- Additional anomalies:
  - **Facial (80%)**: hypotelorism, cyclopia, proboscis, anophthalmia, cleft lip/palate
  - **Intracranial**: absent septum pellucidum, ACC, pituitary hypoplasia, neuronal migration abnormalities, hydrocephalus
  - Other anomalies if syndromic, chromosomal

*Images of Holoprosencephaly at different stages*

*Huang J, et al. Semin Fetal Neonat Med 2012;17:341-346*
Holoprosencephaly (HPE)

- **Environmental:** diabetes (1% risk), teratogens
- **Genetic**
  - **Chromosomal:** 32-41%
    - Trisomy 13: 75%
    - Triploidy: 20%
    - Trisomy 18: 1-2%
    - Prenatal CMA: Clinically significant CNV in >10% with normal karyotype
  - **Syndromic:** 18-25%
    - 10% cholesterol biosynthesis abnormality (Smith-Lemli-Opitz syndrome)
  - **Isolated (non-syndromic):** Autosomal dominant forms
    - microform can be present in parent (single incisor)

# Holoprosencephaly (HPE)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Phenotype OMIM number</th>
<th>Chromosome location</th>
<th>Gene</th>
<th>Gene OMIM number</th>
<th>Inheritance</th>
<th>Animal model</th>
<th>Associated features</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Pseudotruncus lissencephaly</td>
<td>264410</td>
<td>13q32, 5q21</td>
<td>SHH</td>
<td>605651</td>
<td>AR</td>
<td>None</td>
<td>Polydactyly, vertebral septal defect, microphthalmia</td>
<td>Koolen et al.</td>
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<tr>
<td>Pallister-Hall syndrome</td>
<td>146510</td>
<td>7q14.1</td>
<td>ZIC2</td>
<td>605240</td>
<td>AD</td>
<td>None</td>
<td>Hypothalamic hamartoma, hypopituitarism, polydactyly</td>
<td>Johnston et al.</td>
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<tr>
<td>Smith-Lemli-Opitz</td>
<td>270400</td>
<td>11q13.4</td>
<td>SIX3</td>
<td>602838</td>
<td>AR</td>
<td>Mouse, rat</td>
<td>Microcephaly, postnatal developmental delay</td>
<td>Yu et al.</td>
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<tr>
<td>Velocardiofacial</td>
<td>192430</td>
<td>22q11.21</td>
<td>TGIF1</td>
<td>602034</td>
<td>AD</td>
<td>Mouse</td>
<td>Cleft palate, congenital heart disease, short stature</td>
<td>Paylor et al.</td>
</tr>
</tbody>
</table>

**Gene**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>% HPE with pos fam Hx</th>
<th>Simplex cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHH</td>
<td>7q36</td>
<td>30-40%</td>
<td>&lt;5%</td>
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<tr>
<td>ZIC2</td>
<td>13q32</td>
<td>5%</td>
<td>2%</td>
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<tr>
<td>SIX3</td>
<td>2p21</td>
<td>1.3%</td>
<td>rare</td>
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<tr>
<td>TGIF1</td>
<td>18p11.3</td>
<td>1.3%</td>
<td>rare</td>
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<tr>
<td>GLI2</td>
<td>2q14</td>
<td>unknown</td>
<td>unknown</td>
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<tr>
<td>PTCH1</td>
<td>9q22.3</td>
<td>unknown</td>
<td>unknown</td>
</tr>
<tr>
<td>DISP1</td>
<td>1q42</td>
<td>rare</td>
<td>rare</td>
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**Additional Genes**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>% HPE with pos fam Hx</th>
<th>Simplex cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR8</td>
<td>10q24</td>
<td>rare</td>
<td>rare</td>
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<tr>
<td>FOXH1</td>
<td>8q24.3</td>
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<td>rare</td>
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<td>NODAL</td>
<td>10q22.1</td>
<td>rare</td>
<td>rare</td>
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<td>TDGF1</td>
<td>3p23-p21</td>
<td>rare</td>
<td>rare</td>
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<td>GAS1</td>
<td>9q21.33</td>
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<td>rare</td>
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<tr>
<td>DLL1</td>
<td>6q27</td>
<td>rare</td>
<td>rare</td>
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<tr>
<td>CDON</td>
<td>11q24.2</td>
<td>rare</td>
<td>rare</td>
</tr>
</tbody>
</table>

**References**


**Multiple genes**

**Karyotype/CMA**

**Panels Exomes**
Classification of Cortical Malformations

Defects in proliferation
- Somatic mutations
  - Hemimegalencephaly
- Germline mutations
  - Microcephaly

Defects in migration
- Listencephaly
- Neurons
- Migrating neuron
- Neuroprogenitor

Defects in connectivity
- Autism
- Intellectual disability

Defects in Proliferation

• Microcephaly
  – Primary microcephaly
  – Many genes (MCPH loci)
  – Centrosomal and pericentriolar proteins
  – Can be prenatal onset and postnatal onset
  – Can be associated with other abnormalities

• Megalencephaly
  – Global megalencephaly primary or secondary (overgrowth)
  – Hemimegalencephaly
  – Focal cortical dysplasias
  – Role of PI3K-AKT-mTOR pathway activation
  – Somatic mosaic mutations; second hit (TSC)

Microcephaly

- Congenital microcephaly:
  - HC <2SD or <3SD
    - Primary microcephaly (MCPH)
    - Microcephalic primordial dwarfism (MPD): Seckel syndrome, Meier Gorlin syndrome
    - Other: destructive (infection, Zika), environmental (drugs, IR)

- Prognosis:
  - -2SD: 10% intellectual disability
  - -3SD: 50% severe intellectual disability
  - Depends on associated intra- and extracranial anomalies

Microcephaly – Genetic Causes

• Chromosomal abnormalities
• CNVs in 5.4% with normal karyotype
• Multiple genes with fundamental roles in chromosomal segregation and mitotic division - Radial glia cells
  – MCPH: many encode centrosomal proteins involved in centriole biogenesis - chromosomal segregation and mitotic division
  – DNA repair and damage response
  – DNA replication and cilia function
  – Many autosomal recessive forms
Megalencephaly

- Storage in neurons and other cells:
  - Metabolic causes, lysosomal storage disorders

- Overgrowth & other syndromes:
  - Sotos (NSD1): tall, brain anomalies, ID, dolichocephaly
  - Weaver S (EZH2): prenatal overgrowth + brain + other
  - Tuberous sclerosis (TSC1 and TSC2)
  - Simpson-Golabi-Behmel S (GPC3)
  - Bannayan-Riley-Ruvalcaba S, Cowden S (PTEN)
  - Proteus S (mosaic AKT1 mutation): postnatal onset in most; prenatal form with hemimegalencephaly

Megalencephaly

• Segmental brain overgrowth:
  – Hemimegalencephaly and Megalencephaly capillary malformation (MCAP): PIK3CA
  – Megalencephaly-Polymicrogyria-Polydactyly-Hydrocephalus (MPPH): PIK3R2, CCND2, AKT3

• Mosaic mutations:
  – Can be challenging to detect prenatally
  – Cultured cells: proliferative advantage

Tuberous Sclerosis

• Prenatal features:
  – Cortical tubers – 70%
  – Subependymal nodules – 90%
  – Cardiac rhabdomyoma (single or multiple; can resolve)
  – Clinical variability
  – Seizures in 80%
  – Neurodevelopmental (50%) and behavioral impairment

• Genetics:
  – Autosomal dominant; 2/3 are de novo mutations
  – 85% of individuals with criteria for TS have mutations:
    • 31% in TSC1
    • 69% in TSC2 - more severe
    • Germline (5%) and somatic (1%) mosaicism

Malformations of Cortical Development

- **Heterotopias:**
  - Subcortical band heterotopia (SBH)
  - Periventricular heterotopias (PVH)

- **Gyral malformations:** *(postmigrational)*
  - Polymicrogyria (PMG), agyria, pachygyria

- **Lissencephaly:**
  - Classic: type I or Cobblestone: type II

- **Many syndromes:**
  - Combination of above or isolated or + other CNS abnormalities

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PVH at 21w5d

PMG at 35w5d


Bilateral Periventricular Nodular Heterotopia

• Loss of function mutations in Filamin A (FLNA) on Xq28 in 49% but also other causes
  – In 100% of familial cases and in 25% of sporadic cases

• X-linked dominant:
  – Females: variable (mosaic and X-inactivation), Males: prenatal lethal (hypomorph and mosaic mutations possible)

• Other CNS findings:
  – Bilateral nearly contiguous PVH in lateral ventricles, normal appearing cortex, thin corpus callosum, posterior fossa and cerebellar abnormalities

• Manifests as seizure disorder

Polymicrogyria

• 20% of all malformations of cortical development - Difficult to see by ultrasound → Fetal MRI
  – Isolated
  – With other CNS abnormalities
  – With other non-CNS abnormalities

• Non-genetic: infections (CMV, other), ischemia

• Microdeletions
  – Cardiac anomalies + (perisylvian) PMG → think 22q11.2 deletion
  – 1p36, other

• Single gene disorders (multiple genes!)
  – PMG with cysts: think Aicardi S (X-linked - no gene known!)
  – Metabolic/lysosomal, Tubulinopathies

Romero DM
Sequelae of Polymicrogyria

- Epilepsy 78%
- Global developmental delay 70%
- Spasticity (hemiplegia, paraplegia) 51%
- Dysmorphic features 45%
- Arthrogryposis, talipes
- In utero presentation (may increase with MRI) 5%
- Macrocephaly 50%
- Microcephaly 5%
- Hydrocephalus (MCAP, MPPH)

Depends on underlying cause + associated findings

Lissencephaly

- “lissos” (smooth) “enkephalos” (brain)
- 11.7 – 40 / million births
- Classical lissencephaly (type I): 1.2:100,000 births
  - Thick 4-layer cortex, absence of other major brain anomalies
  - Grades 1 – 6: complete agyria (1) to mild (6)
  - Undermigration
- Cobblestone complex (type 2): 1:100,000 births
  - Overmigration
- Variant lissencephaly:
  - lissencephaly with agenesis of the corpus callosum (XLAG)
  - lissencephaly with cerebellar hypoplasia (LCH)
  - microlissencephaly.

Classic Lissencephaly

- Undermigration of neurons
- Agyria or pachygyria
- Three main genes:
  - *LIS1*: 17p13.3
    - Miller-Dieker syndrome
    - Isolated lissencephaly
  - *DCX*: Xq22.3
  - *TUBA1A*: 12q12-14
- Rarer case can be caused by other genes

76% of classic lissencephaly

4% of classic lissencephaly
Cobblestone Cortical Malformation

- Nodular surface: Neuronal overmigration → very disorganized cortex
- Dystroglycanopathies
  - Walker-Warburg syndrome (WWS), muscle-eye-brain disease (MEB), other congenital muscular dystrophies (Fukuyama)
- Other CNS anomalies

Cerebellum and posterior fossa

• 1:5000 live births
• 20-100% impaired neurological outcome – depends on type and associated anomalies

• Primary cerebellar hypoplasia
  – Chromosomal abnormality in 16.3%; abnl CMA in 13.7%
  – Metabolic: Smith-Lemli-Opitz, Mb deficiency, AS deficiency
  – Single gene disorders:
    • Ritscher-Schinzel S: RTSC1/SPG8 (KIAA0196), RTSC2 (CCDC22))
    • Joubert spectrum: multiple genes and loci
    • CHARGE S (mulitple other anomalies): CHD7
    • Acrocallosal S (KIF7); other syndromes

• Secondary: CMV, teratogens, prematurity

Mega-Cisterna magna

- 40% of all prenatally detected posterior fossa abnormalities
- 4th ventricle, cerebellar hemispheres and vermis are normal

**Isolated MCM:**
- 92-100% have normal developmental outcome
- Higher cognitive functions (verbal memory and fluency) may be impaired

**MCM with associated CNS and non-CNS defects:**
- 29% to 2/3 develop normally
- 1/3 cognitive and language and motor delay

Dandy-Walker Malformation

• Complete or partial agenesis of vermis, cystic dilation of 4th ventricle, enlarged posterior fossa with upward displacement of tentorium
• Up to 86% have other abnormalities; 49% other CNS anomaly
• Up to 1/3 develop normally
• With vermis lobulation: 82%-90% have normal IQ;
• Abnormal IQ:
  – Associated CNS or extra-CNS malformations
  – Absent or abnormal vermis lobulation:
• 50% neurological abnormalities
  – 50% hypotonia
  – 42% cerebellar dysfunction
  – 5% hemiparesis

DWM at 34w3d

Vermian hypoplasia and cerebellar hypoplasia/dysgenesis

• Up to 70% with other anomalies
  – Poor prognosis for neurodevelopmental outcome
• Isolated VH:
  – 77% have normal development
  – 23% have neurological abnormalities:
    • Gross and fine motor disability
    • Social and communication defects
    • 15% behavioral
    • 23% hypotonia
  – Isolated CH:
    • Worse outcome than VH

Joubert Syndrome and Related disorders

• **Molar tooth sign:**
  – Abnormally deep interpeduncular fossa
  – Enlarged superior cerebellar peduncles, more horizontally oriented
  – Hypoplastic cerebellar vermis

• **Associated anomalies:** renal, hepatic, eye, polydactyly

• **Overlap with other conditions**
  – Meckel syndrome -- Hydrolethalus syndrome
  – Nephronophtisis -- Acrocallosal syndrome
  – Bardet Biedl -- Orofacial digital syndrome

• **Developmental delays, hypotonia, breathing anomalies, ataxia abnormal eye movement, and facial dysmorphia**

Joubert syndrome
NIH cohort mutated genes

- Multiple genes: ciliopathies molecular diagnosis in 62-94%:
- autosomal recessive mutation in >33 genes
- 1 X-linked gene

Genetic and other testing

• Karyotype / chromosomal microarray beneficial for most findings
• Gene panel sequencing versus whole exome sequencing
• Amniocyte culture for suspected somatic mutations PIK3CA overgrowth syndromes
• Infection testing: CMV, Toxoplasmosis, Zika
  – HSV1/2 and syphilis much lower yield

Thank you

QUESTIONS?

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