CONGENITAL DISORDERS

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Question Based Learning
Lecture Modules

- Skull & CNS Malformations
- Developmental Issues
- Neurocutaneous Syndromes

Module: Skull & CNS Malformation

Craniosynostosis

Skull deformities associated with single suture synostosis

**Craniosynostosis cont’d**

- Incidence .04% - .1%, usually sporadic
- Primary 2%-8%
  - Sagittal 50%-58% > scaphocephaly
  - Coronal 20%-30% > frontal plagiocephaly, unil.
  - Metopic 4%-10% > trigonocephaly
  - Lambdoid 2%-4%
- Syndromic: genetic 21% with 86% single gene, 15% chromosomal
  - FGFR2 on chr 10 (32%) AD: Apert, Pfeiffer, Crouzon
  - FGFR3 (25%) AD: Muenke and Crouzon with acanthosis nigrans
  - TWIST 1 (19%) AD: Saethre-Chotzen
  - EFNB1 (7%) X-linked: craniofrontonasal syndrome, worse in females
- Secondary: due to lack of brain growth


**Causes of Microcephaly**

- Infection
  - In utero
  - Postnatal
- In utero drug exposure
- Hypoxic ischemic encephalopathy
- CNS malformation
- Chromosomal anomalies
- Familial

**Causes of Macrocephaly**

- Increased fluid spaces
  - Subdural effusions/hematoma
  - Hydrocephalus
- Familial macrocephaly
- Megalencephaly
- Primary diseases of bone
- Sotos syndrome = cerebral gigantism
  - Devel delay, epilepsy, corpus callosum agenesis, hypotonia, Wilms tumor
- Riley-Smith syndrome = Bannayan-Riley-Ruvalcaba syn
  - 10q23.3 PTEN, pseudopapilledema, multiple hemangiomata

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**Notes:**
Aqueductal Stenosis

Figure 2 Cardiac-gated cine-MRI and axial FLAIR-weighted images pre- and postoperative cardiac-gated cine-MRI images (A vs. B, respectively) demonstrate the absence of CSF flow across the aqueduct of Sylvius and turbulent flow in the third ventricle following ventriculostomy.


Posterior Fossa Tumors

- 54%-70% of all childhood brain tumors
- Medulloblastoma
- Ependymoma
- Pineoblastoma
- Primitive neuroectodermal tumor (PNET’s)
- Astrocytoma of the cerebellum and brainstem


Benign Extra Axial Collections of Infancy

- Macrocephaly
- Excessive extra-axial fluid
- Mild ventriculomegaly
- Normal development
- Chronic subdural hematoma or hygroma, may require subdural puncture or subdural peritoneal (SDP) shunt
- Head growth usually levels off by 24 months

Benign Extra Axial Fluid Spaces of Infancy

Fig. 5: Images obtained from an infant with benign extracerebral collections of infancy and spontaneous subdural hemorrhage. Axial T2, T1, GRE, and FLAIR images (left to right) show CSF-intensity frontal subarachnoid collections at birth (top row). At 26 days postnatal age (bottom row), superimposed subdural collections that don’t conform to CSF signal are present (courtesy of Veronica J. Rooks, MD, Tripler Army Medical Center, Honolulu HI)

P. Barnes, Stanford University.

Evaluation for Subdural Hemorrhages

- CBC, chem 12
- INR, PTT
- Factor XIII assay
- Platelet function assay
- Von Willebrand workup (von Willebrand antigen, ristocetin cofactor, factor VIII)
- Urine organic acids
- Skeletal survey
- Ophthalmology evaluation

Glutaric Aciduria Type 1

Fig. 19: Images obtained from a 9 month-old male infant with glutaric aciduria type 1, SDHs, and RHs. CT (A), T1 (B), FLAIR (C), and T2 (D) MRI images show bilateral mixed-density and mixed-intensity extracerebral collections with fluid levels and septations, especially on the left side. Other characteristic findings for glutaric aciduria type 1 include bilaterally wide sylvian fissures (arachnoid cysts) plus abnormal basal ganglia (globus pallidus) and cerebral white matter intensities (arrows)

P. Barnes, Stanford University.

- 1 per 30,000 to 40,000 AR 19p13.2
  - More in Amish
  - More in Ojibwa (Canada) up to 1 in 300 newborns
- Glutaryl-CoA dehydrogenase (GCDH) gene
- Necessary to process lysine, hydroxylysine and tryptophan

Glutaric Aciduria Type 1 cont’d

Megalencephaly or Macroencephaly
- Abnormally large and heavy brain
- Usually malfunctioning
  - Developmental delay
  - Seizures
  - Corticospinal tract signs
- May be seen with metabolic diseases
  - Leukodystrophies
  - Lipidoses
  - Mucopolysaccharidoses
- May be seen with neurocutaneous syndromes
  - Neurofibromatosis
  - Tuberous sclerosis
  - Sturge-Weber syndrome
  - Klippel-Trenaunay-Weber syndrome

CNS Malformations
- Destructive lesions
- Midline defects
  - Neural tube defects
  - Other midline defects
- Other lesions
  - Cerebral hemispheres
  - Posterior fossa malformations

Embryology
- Week 4 (2 weeks from fertilization - first missed menstrual period)
  - A notochord forms in the center of the embryonic disk
- Week 5 (3 weeks from fertilization)
  - The neural tube closes
- Week 6 (4th week of development)
  - The brain divides into 5 vesicles, including the early telencephalon
- Week 28 (26th week of development)
  - The brain develops rapidly.
  - The nervous system develops enough to control some body functions
  - The eyelids open and close

Source:
Intraventricular Hemorrhage

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Subependymal region and/or germinal matrix</td>
</tr>
<tr>
<td>II</td>
<td>Grade I with extension into lateral ventricles</td>
</tr>
<tr>
<td>III</td>
<td>Grade II with ventricular enlargement</td>
</tr>
<tr>
<td>IV</td>
<td>Intraparenchymal hemorrhage</td>
</tr>
</tbody>
</table>

Source: www.hawaii.edu/medicine/pediatrics/pemxray/v5c07n.jpg.

Porencephalic Cyst


Porencephaly


Hydranencephaly

Source: http://www.nature.com/eye/journal/v22/n5/images/6703058f1.jpg.

Neural Tube Defects

<table>
<thead>
<tr>
<th>Type</th>
<th>Incidence</th>
<th>Associated Risk Factors</th>
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<tbody>
<tr>
<td>Anencephaly</td>
<td>1-10/1000*</td>
<td>Folate deficiency 50%-70% reduced risk</td>
</tr>
<tr>
<td>Encephalocele</td>
<td></td>
<td>Maternal hyperthermia</td>
</tr>
<tr>
<td>Spina bifida</td>
<td></td>
<td>Maternal diabetes</td>
</tr>
<tr>
<td>Valproate</td>
<td></td>
<td>Maternal drug exposure</td>
</tr>
<tr>
<td>Opiates OR</td>
<td></td>
<td>ベンゼン</td>
</tr>
</tbody>
</table>

** 2 PMID: 21345403
Neural Tube Defects: Genetic Risks
- LEPR (leptin receptor) rs1805134 minor C allele genotype relative risk (GRR): 1.5
- COMT (catechol-O-methyltransferase) rs737865 major T allele GRR: 1.4
- 5,10-methylenetetrahydrofolate reductase, MTHFR 677C>T homozygosity OR: 1.3
- T (Brachyury) rs3127334 major A allele OR: 2.4
- LEPR (leptin receptor) rs1137100 (K109R) major A allele GRR: 1.4
- PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) haplotype combinations with high-transcriptional activity OR: 1.5

Source: Carter, TC 2010; PMID: 21204206.

Anencephaly

Source: http://drugster.info/img/ail/2107_2120_2.jpg.

Encephalocele

Source: craniofacialfoundation.org/images/photos/fig1.jpg.

Encephalocele cont’d

Source: http://3.bp.blogspot.com/_oAQI4j4B9Zc/SHxmJq7OlOI/AAAAAAAhs/kKMEjpiXZCU/s1600/diastematomyelia.jpg.

Spina Bifida
- Types
  - Myelomeningocele 1 in 800
  - Meningocele
  - Spina bifida occulta – may be asymptomatic
- Cutaneous manifestations
  - Hairy patch
  - Nevus
- Variable bowel and bladder dysfunction
- Variable sensorimotor dysfunction
- Other associations
  - +/- Cognitive impairment
  - +/- Epilepsy
  - +/- Hydrocephalus

Spinal Cord Anomalies
- Spina bifida
- Diastematomyelia
- Syringomyelia

Source:

Source:
http://3.bp.blogspot.com/_oAQR4j4B9Zc/SHxmJq7OI0I/AA AAAAAAh/s/kKMEjpiXZCU/s1600/diastematomyelia.jpg
Spinal Cord Anomalies *cont’d*

Source: commons.wikimedia.org/wiki/File:Syringomyelia.jpg.

Midline Defects *cont’d*


**Midline Defects**

- Holoprosencephaly
- Agenesis of the corpus callosum
- Septo-optic dysplasia

**Question:** An in utero ultrasound shows the fetus has holoprosencephaly. There is a family history of both holoprosencephaly and schizencephaly. What is the most likely cause of the fetus’ CNS malformation?

A. CMV infection in utero  
B. Environmental toxin  
C. Maternal diabetes mellitus  
D. Sonic hedgehog mutation  
E. Trisomy 13

**Midline Defects**

Source: [http://25.media.tumblr.com/tumblr_lib3flWx1h1qa6reo1_500.jpg](http://25.media.tumblr.com/tumblr_lib3flWx1h1qa6reo1_500.jpg)

**Holoprosencephaly**

Source: [http://www.peds.ufl.edu/PEDS2/research/debusk/images/5_63.jpg](http://www.peds.ufl.edu/PEDS2/research/debusk/images/5_63.jpg)

<table>
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<th>Semilobar</th>
<th>Lobar</th>
<th>MIH</th>
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<tr>
<td>Corpus callosum</td>
<td>Absent</td>
<td>+ splenium</td>
<td>+/- ant body + splenium</td>
<td>+/- genu + splenium</td>
</tr>
<tr>
<td>Ventricles</td>
<td>Monoventricle</td>
<td>- Ant. horns</td>
<td>Rudimentary ant. horns</td>
<td>Normal or hypo ant. horns</td>
</tr>
<tr>
<td>Dorsal cyst</td>
<td>Usually</td>
<td>+/-</td>
<td>Absent</td>
<td>+ in ¼</td>
</tr>
<tr>
<td>Thalamus</td>
<td>Often fused</td>
<td>Partial fusion</td>
<td>Used. separated</td>
<td>Fused in ⅓ to ½</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>Often fused</td>
<td>Partial fusion</td>
<td>Variable fusion</td>
<td>Separated</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>100% w/ fusion</td>
<td>98% w/ fusion</td>
<td>83% w/ fusion</td>
<td>Separated</td>
</tr>
</tbody>
</table>

Source: Hahn, J. et. al, 2010; *PMID*: 20104607
Alobar Holoprosencephaly

Source:

Semilobar Holoprosencephaly

Source:

Lobar Holoprosencephaly

Source:

Middle Interhemispheric Variant (MIH)

Source:

Holoprosencephaly
- 1/250 fetuses or 1/10,000 live births
- Pituitary dysfunction
- Optic and olfactory problems:
  - Cyclopia, hypotelorism, proboscis
- 80% facial anomalies
  - Cleft lip/palate, single incisor
- Epilepsy
- Hydrocephalus
- Neural tube defects: spina bifida
- 10% defect in cholesterol biosynthesis
- Maternal diabetes mellitus 1% risk (200x normal)
- Association with alcohol and retinoic acid in animals
- Association with cholesterol lowering agents
  - Statins
- Genetic 25%-50%
  - Syndromic 18%-25%
    - Trisomy 13, trisomy 18, triploidy
    - AD: Pallister-Hall, Rubenstein-Taybi, Kallman, Martin, Steinfeld
    - AR: Pseudotrisomy 13, Smith-Lemli-Opitz, Meckel, Genoa,
    - Lambotte, Hydrolethalus
  - Nonsyndromic 75%-82%
  - Other: caudal dysgenesis

Nonsyndromic Genetic Causes of Holoprosencephaly: AD

- Sonic hedgehog (SHH) 7q36 - HPE3
  - 30%-40% +FH, can also cause schizencephaly
- Zinc finger protein of cerebellum 2 (ZIC2) 13q32- HPE5
  - 5% +FH
- Sine oculis homeobox, drosophila, homolog of, 3 (SIX3) 2p21 - HPE2
  - 1.3% +FH, can also cause schizencephaly
- Transforming Growth Factor Beta induced Factor (TGIF1) 18p11.3 semilobar - HPE4
  - 1.3% +FH
- Gli-Lruppel family member 2 (GLI2) 2q14 - HPE9
- Patched, drosophilam homolog of, 1 (PTCH1) 9q22.3 - HPE7
  - Can also cause basal cell nevus syndrome
- 21q22.3; autosomal recessive and autosomal dominant HPE1


Colpocephaly

Source: http://imaging.birjournals.org/content/vol16/issue2/images/large/IMJ52494-4.jpeg.

Agenesis of the Corpus Callosum

Source: http://3.bp.blogspot.com/_P-Qq1L9TbEl/Sjm77WaiTI/AAAAAAAXk/cPKU23-hScw/s400/cc-missing.bmp.

- 630 cases in 3.4 million live births in California from 1983-2003
  - Isolated
  - Associated with other anomalies CNS 49.5%
    - Dandy Walker
    - Andermann syndrome 15q13 AR SLC12A6 gene
      - Sensorimotor neuropathy (incl CN), tremor, MR
    - Schizencephaly
    - Holoprosencephaly
    - Aicardi syndrome X linked?
      - Agenesis of CC, Epilepsy (infantile spasms), retinal lacunas
  - Musculoskeletal 33.5%
  - Cardiac 27.6%
  - Midline defects

Source: Glass/HC, et al. 2008, PMID: 18642362
Septo-optic Dysplasia

- Optic nerve hypoplasia
- Midline defects
  - Agenesis of septum pellucidum
  - Corpus callosum hypoplasia or absence
  - Pituitary deficiencies
- Associations
  - Poor vision
  - Developmental delay
  - Epilepsy
  - Sleep disturbance
  - Precocious puberty

Source: http://www.nature.com/ejhg/journal/v18/n4/thumbs/ejhg2009125f2th.jpg.

Schizencephaly

- California from 1985 to 2001
  - 1.54 in 100,000
  - Non-CNS abnormality in 1/3 of cases
    - Over half of which could be classified as secondary to vascular disruption, including gastrochisis, bowel atresias, and amniotic band disruption sequence
- Genetic
  - EMX2 (10q26.1), SIX3 (2p21), SHH (7q36)

Source: http://www.mir.wustl.edu/neurorad/graphics/assets/images/Le arning_Files/130A617F1C92DB5B.JPG.

Other Brain Malformations

- Cerebral hemispheres
  - Schizencephaly
  - Pachygyria
  - Polymicrogyria
  - Lissencephaly
  - Double cortex
  - Hemimegencephaly
- Posterior fossa malformations
  - Cerebellar malformations
  - Other

Source: Fard, MA, 2010; PMID: 21037540

Pachygyria

Pachygyria cont’d


Polymicrogyria

Source: http://jmg.bmj.com/content/42/5/369/F6.large.jpg.

- Bilateral frontal (BFP)
- Bilateral frontoparietal (BFPP)
  - Dysconjugate gaze, cerebellar signs
- Bilateral perisylvian (BPP)
  - Pseudobulbar signs
- Bilateral parasagittal parietooccipital (BPPOP)
- Bilateral generalized (BGP)
- Unilateral perisylvian (UPP)
- Infection
  - CMV, toxoplasmosis, syphilis, VZV
- Hypoxia
- Genetic
  - Deletion 22q11.2
  - X linked
  - GPR56 gene (16q13) AR: bilateral frontoparietal
- Often with DD, MR, epilepsy and CP

Lissencephaly


Double Cortex


Lissencephaly

- LISX1: Xq22.3-q23 DCX
  - Associated with agenesis of corpus callosum and double cortex in female
- LISX2: Xp22.13 ARX
  - Ambiguous genitalia
- LIS1: 17p13.3 (may also have double cortex)
- LIS2: 7q22
- LIS3: 12q12-q14 autosomal dominant
- Miller-Dieker Lissencephaly Syndrome (MDLS): 17p13.3
  - Autosomal dominant
  - Infantile spasms
  - Omphalocele, duodenal atresia
  - Congenital heart defects
- Infection before 16-18 wks
Miller-Dieker Syndrome


**Hemimegalencephaly**
- One hemisphere is abnormally large
- Form of cortical dysplasia
  - Epidermal nevus syndrome
  - Hypomelanosis of Ito
- Epilepsy, often intractable
- May need hemispherectomy for seizure control

Source: http://www.med.uc.edu/neurorad/webpage/corken1.jpg.

**Posterior Fossa Malformations**
- 1/5000 live births
- Pontocerebellar hypoplasia
- Cerebellar disruptions
- Cerebellar malformations
  - Dandy-Walker malformation
  - Joubert syndrome
  - Rhombencephalosynapsis
- Other posterior fossa malformations
  - Chiari malformation

Source: Bolduc ME, 2011; PMID: 21418200.

**Cerebellar Disruptions**
- Global cerebellar hypoplasia
  - Chromosomal: trisomy 9, 13 and 18
  - Disorders of glycosylation
  - Teratogens: anticonvulsants, cocaine
  - Infection: CMV
- Unilateral hypoplasia: can be seen at 20-24 wks
  - Misoprostol
- Cerebellar cleft usu. due to hemorrhage
- VLBWP <1500 g, before 28-32 wks

**Question:** A 3 y.o. boy comes to clinic with a history of abnormal jerky eye movements, irregular breathing, hypotonia, ataxia, behavior problems and fibrosis of the kidney. His MRI is on the right. What is the most likely diagnosis?

A. Dandy-Walker syndrome
B. Holoprosencephaly
C. Joubert syndrome
D. Lissencephaly
E. Septo-optic dysplasia

**Pontocerebellar Hypoplasia**
- Inherited, progressive disorders, may have onset in utero
- Up to 7 subtypes
  - Mitochondrial tRNA splicing endonucleases PCH2, PCH4, PCH5
  - Nuclear mitochondrial arginyl tRNA synthetase PCH6 and PCH1 (along with vaccinia related kinase 1)
- Progressive microcephaly
- Severe cognitive and motor handicaps
- Seizures
- Only symptomatic treatment
- Poor prognosis, most die during infancy or childhood


Notes:
Dandy-Walker Syndrome

Dandy-Walker Malformation (DWM)
- 1/5000 live born
- Partial or complete agenesis of vermis
- Cystic dilation of 4th ventricle with enlarged posterior fossa and superior displacement of cerebellum (not in DW variant)
- Hydrocephalus (not in DW variant)
- 1/3 normal development

Source: Donkelaar, T, 2009; PMID: 19732611.

Dandy-Walker Syndrome
- Cause unknown
- Chromosome 3q24 deletion
  - ZIC1 and ZIC4
- Trisomy 9
- Trisomy 13
- Trisomy 18
- Multiple other chromosomal anomalies reported


Molar Tooth Sign


Joubert Syndrome
- 1/100,000
- Most autosomal recessive, some X-linked, more than 8 genes
- 6 subtypes
  - Pure, with ocular, with renal, with oculorenal, with hepatic, with orofaciiodigital
- Ataxia
- Hypotonia
- Abnormal jerky eye movements
- Breathing dysregulation
- Dysmorphic
  - Prominent forehead, upturned nose, open mouth
- Mental retardation
- Behavioral problems
- Poor prognosis, 5 year survival 50%

Source: Donkelaar, T, 2009; PMID: 19732611
Brancati, F; 2010; PMID: 20615230
Parisi, MA, 2009; PMID: 19876931.
Rhombencephalosynapsis

- Vermis hypoplasia
  - Absence of anterior vermis
  - Deficiency of posterior vermis
- Fusion of cerebellar hemispheres
  - May have fusion of dentate nuclei and middle cerebellar peduncles
- Diamond shaped fourth ventricle
- Dysgenesis of corpus callosum
- May have fused thalami

Chiari Malformation

**Cont’d**

Source: http://www.ajnr.org/cgi/reprint/19/3/547.pdf.

- **Chiari Malformation**
  - **Type 1**
    - May be autosomal dominant
    - 1 in 1,250
    - Protrusion of cerebellar tonsils through foramen magnum of 5 mm or more
    - 80% with syringomyelia
  - **Type 2**
    - Inferior cerebellar vermis, cerebellar hemispheres, pons, medulla, and fourth ventricle through foramen magnum
    - Myelomeningocele

Module: Developmental Issues

**Question:** Which developmental milestone is a typically developing child expected to acquire LAST?

- A. Copy a square
- B. Follow a 3-step command
- C. Perform a tandem gait
- D. Throw overhand
- E. Unbutton his/her clothes


Notes:


Comprehensive Review of Neurologic and Psychiatric Disorders: Congenital Disorders
Celia Chang © 2011-2012 BeatTheBoards.com 877-225-8384
Developmental Milestones

- Motor
  - Fine motor
  - Gross motor
- Self help
- Cognitive/academic
- Social/emotional
- Language
  - Receptive
  - Expressive

Gross Motor Milestones I
- Start in midline from top down
  - 1 month chin up
  - 2 months chest up
  - 3 months props on forearms
  - 4 months props on wrists
  - 6 months props on hands


Gross Motor Milestones II
- 4 months rolls front to back
- 5 months rolls from back to front
- 7 months sits without support
- 9 months pulls to stand
- 10 months cruises with 2 hands
- 12 months independent steps
- 15 months climbs on furniture
- 24 months throws overhand
- 2 years 4 months walks on toes after demo
- 6 years tandem walks


Language Milestones I
- 5 months begins to respond to name
- 6 months stops momentarily to “no”
- 8 months responds to “come here” says “mama” nonspecific
- 10 months says “dada” specific waves bye bye
- 11 months says first word
- 12 months points follow 1 step command w/ gesture


Language Milestones II
- 14 months Follow 1 step command w/o gesture
- 20 months Says “no”
- 24 months 2 word sentences follows 2 step command parallel play
- 2 years 6 months imitates adult activities
- 3 years puts on shoes unbuttons 3 word sentences
- 4 years follows 3 step commands


Drawing
- 2 year old Draw horizontal line
- 3 year old Copy circle
- 4 year old Copy cross
- 5 year old Copy square
- 6.5 year old Copy triangle
- 7.5 year old Copy diamond
- Draw a person: body parts, clothes, etc

Abnormal Development
- Vision
- Speech
- Cognitive


Vision
- Acuity
- Strabismus
  - Exo vs. eso
  - Tropia vs. phoria
- Amblyopia
Language
- Auditory testing
- Mental retardation
- Autism

Question: A newborn fails the hearing screen and is found to have congenital hearing loss. What else should the child be screened for?
A. Autism
B. Panhypopituitarism
C. Polycystic kidneys
D. Prolonged QT
E. Spina bifida

Hearing Loss
- 1.2-1.7 cases per 1000 live births
  - 20%-30% profound hearing loss >90 dB
- 30% with additional disability
  - Cognitive impairment
- Site
  - Conductive
  - Sensorineural
  - Neural
  - Central
- Onset
  - Congenital
  - Acquired
- Universal neonatal screening
  - Otoacoustic emissions
  - Auditory brain stem responses


Hearing Loss cont’d
- Causes (30%-40% unknown)
  - Infectious
    - In utero: CMV, rubella, sphi lis, toxo, viral
    - Postnatal: measles, mumps, meningitis, sepsis
  - Ototoxic drugs
    - Aminoglycoside antibiotics (with the 1555A→G mutation of the 12S rRNA [MTRNR1] gene confers susceptibility
    - Chemotherapeutic agents e.g., Cisplatin
  - Environmental
    - Extracorporeal membrane oxygenation
    - Noise
  - Misc
    - Craniofacial anomalies
    - Prematurity
    - Low birth weight
    - Anoxia
    - Rhesus incompatibility


Genetic Hearing Loss
- At least 50%
- Inheritance, usu. AR (80% of cases) but may be AD (15%), X-linked or mitochondrial (<1%)
- Gap-junction protein connexin 26 (a GJB2 mutation)
- Motor molecules (actin and myosin)
- Transcription factors
- 4% inner-ear malformation


Syndromic Hearing Loss
- 400 syndromes
- Usher’s syndrome
  - AR mult types/genes
  - Also retinitis pigmentosa and vestibular dysfunction
- Pendred’s syndrome
  - AR 7q31
  - Also thyroid and vestibular dysfunction
- Jervell and Lange-Neilsen 1
  - AR 11p15.5 KCNQ1 gene
  - Prolonged QT

**Congenital Deafblindness**
- 74% with mental or behavioral diagnosis
- 34% mental retardation
- 13% psychosis

Source: Dammeyer, J, 2011; PMID 21227639.

**Mental Retardation**

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<th>IQ</th>
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<td>Profound</td>
<td>Below 20</td>
<td>1%-2%</td>
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<tr>
<td></td>
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<td>Basic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>commands</td>
</tr>
<tr>
<td></td>
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<td>and requests at best,</td>
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<td></td>
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<td>maybe some self care</td>
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<td>Severe</td>
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<td>Very basic self care and communication,</td>
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<td>may be able to live in group homes</td>
</tr>
<tr>
<td>Moderate</td>
<td>35-49</td>
<td>10%</td>
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<tr>
<td></td>
<td></td>
<td>Can work and do self care with moderate supervision, can live in group homes</td>
</tr>
<tr>
<td>Mild</td>
<td>50-69</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Up to 6th grade level, can sometimes live independently</td>
</tr>
<tr>
<td>Borderline</td>
<td>intellectual functioning 70-79</td>
<td></td>
</tr>
</tbody>
</table>


- Down syndrome most common genetic form
- Fragile X most common inherited form
- Fetal alcohol most common form due to teratogen
- Phenylketonuria most common metabolic disorder
- Lead poisoning important postnatal
- Psychosocial
- No identified cause in 30% severe and 50% mild
- 40%-70% with diagnosable psychiatric disorder


**Autism**
- Qualitative impairment in social interaction
- Qualitative impairment in communication
- Restrictive repetitive and stereotypic patterns of behavior
- Indications for immediate evaluation
  - No babbling, pointing or gesture by 12 months
  - No single words by 16 months
  - No spontaneous 2 word phrase by 24 months
  - Any loss of any language or social skills at any age


**Kernicterus**
- Very rare: 5 cases per year in US
- Early
  - Jaundice: bilirubin >20-25 mg/dL
  - Lethargy
  - Bulging fontanelle
  - Seizures
  - Opisthotonus
- Late
  - High frequency hearing loss
  - Mental retardation
  - Spasticity
  - Movement disorder: athetosis
- Imaging: high intensity of globus pallidus on T2 MRI


**Cerebral Palsy**
- Nonprogressive brain lesions involving motor or postural abnormalities that are noted early in development
  - Less than 3 years of age
  - Abnormality of movement or posture
  - 70%-80% prenatal etiology

**Associated Findings**
- 30%-50% with mental retardation
- 15%-60% with epilepsy
- Oral motor problems
  - Speech and language problems
  - Failure to thrive
- Constipation
- Visual and hearing problems
  - Strabismus

Notes:
Types of Cerebral Palsy

- Spastic 80%
  - Spastic hemiplegia
  - Spastic diplegia
  - Spastic quadriplegia
- Dyskinetic
- Ataxic
- Hypotonic: truncal and extremity hypotonia with hyperreflexia and persistence of primitive reflexes
- Mixed

Differential Diagnosis

- Progressive disorder
  - Inborn error of metabolism
  - Genetic conditions
- Spinal cord abnormality
  - Tetheredcord
  - Spinal cord malformation
- Hereditary spastic paraplegia
- Dystonia

Evaluation for Cerebral Palsy

- History with family history
- Neurological exam
- Brain MRI
- Spine MRI

Treatment - Medication

- Baclofen (Kemstro and Lioresal)
  - Oral vs. G tube
  - Intrathecal
- Clonazepam (Klonopin, Ravotril, Rivotril)
- Tizanidine (Zanaflex, Sirdalud)
- Dantrolene (Dantrium, Dantrolen)
- Botulinum toxin

Treatment

- Medical devices
  - Hand splint
  - Ankle foot orthotic (AFO)
  - Walker
  - Wheelchair
- Surgery
  - Baclofen pump
  - Achilles tendon lengthening
  - Hip adductor release

Neurocutaneous Syndromes

Neurocutaneous syndrome

- Neurofibromatosis I
- Neurofibromatosis II
- Tuberous sclerosis
- Incontinentia pigmenti
- Sturge-Weber syndrome
- Ataxia-telangiectasia
- Von Hippel-Lindau disease
- Hypomelanosis of Ito
- Linear sebaceous nevus syndrome
- Klippel-Trenaunay-Weber Syndrome

Question: A 25 y.o. woman without previous health problems develops a spontaneous pneumothorax. On exam, she has hypopigmented macules on her extremities and a flesh colored, raised patch on her back. What is the most likely diagnosis?

A. Hypomelanosis of Ito
B. Incontinentia pigmenti
C. Linear sebaceous nevus syndrome
D. Tuberous sclerosis
E. Von Hippel-Lindau disease

Café Au Lait Spots

Source: http://www.hindsdale86.org/staff/kgabric/Disease09/neurofibromatosis%20type%201/nuro%201.jpg.
**Pseudoarthrosis**


**Axillary Freckles**

Source: [http://bjr.birjournals.org/content/vol78/issue931/images/medium/BJR57811-12.gif](http://bjr.birjournals.org/content/vol78/issue931/images/medium/BJR57811-12.gif).

**Neurofibromatosis I**

*Von Recklinghausen disease*

Fig. 8-13-1 Lisch nodules in neurofibromatosis type 1


- 1/3000
- 50% spontaneous mutation
- Autosomal dominant, 17 q11.2
- Neurofibromin tumor suppressor which suppresses products of ras

**Neurofibromatosis I: Need 2**

- Café au lait spots >/= 6 (5 mm vs. 15 mm)
- Neurofibromas >/= 2 ( or 1 plexiform)
- Freckles – axillary or inguinal
- Optic glioma
- Lisch nodules >/= 2
- Osseus lesion
  - Sphenoid dysplasia
  - Cortical thinning of long bone, pseudoarthrosis
- First degree relative
Neurofibromatosis I
- Risk for malignancy
  - Fibrosarcoma
  - Leukemia
  - Pheochromocytoma
  - Rhabdomyosarcoma
  - Wilms tumor
- Aortic and renal artery stenosis
- Endocrine abnormalities
  - Precocious puberty
  - Growth hormone deficiency: short stature
- Mental retardation
- Epilepsy

Neurofibromatosis II

Source: http://www.massgeneral.org/cancer/assets/images/thumb/th_spring_story3-1.gif.

- 1/35,000 live births
- Autosomal dominant, 22q11-13.1
  - Schwannomin/merlin proteins
  - Gardner (splice/missense) vs. Wishart (frameshift/nonsense)
- 50%-70% spontaneous mutation
- Bilateral 8th cranial nerve schwannoma
- First degree relative + unilat before 30 years
- 2 of neurofibroma, meningioma, glioma, schwannoma, juvenile posterior subcapsular opacity
- Cutaneous lesions 70%, usu <3
- No axillary/inguinal freckles or Lisch nodules

Notes:
Tuberous Sclerosis

Source: http://www.ajronline.org/content/vol85/issue4/images/small/0_04_1906_02d.gif.

Subependymal Giant Cell Astrocytoma (SEGA)

Source: http://4.bp.blogspot.com/_29vl4MXQ-A/TPKk8Q9-7MI/AAAAAAAAlI0/vXIOMZA2Z7s/s1600/SubependymalGiantCellAstrocytoma.jpg.

Pulmonary Lymphangioleiomyomatosis

(B) High resolution chest CT scan of patient 3 showing thin walled cysts throughout the whole lung zones. Note bilateral pneumothoraces with chest tube in the right


Tuberous Sclerosis

- 1/5800 to 1/10,000
- Autosomal dominant
  - TS1 – 9q34: hamartin
  - TSC 2 – 16q13.3 tuberin
- 50% spontaneous mutation
Tuberous Sclerosis cont’d
- Hypomelanotic skin macule = Ash leaf spot
- Shagreen patch: 1-10 cm flesh colored plaque
- Facial angiofibroma = adenoma sebaceum
- Subungual and periungual fibroma = Koenen tumor
- Retinal hamartoma (phacomata)
- Cortical tuber
- Subependymal nodules, including SEGA
- Renal angiomyolipomas in 75%
- Rhabdomyoma 50% in infancy, may regress
- Pulmonary lymphangioleiomyomatosis (LAM)

Recommended
- Brain MRI: every 1-3 yrs until age 18
- EKG and echocardiogram: every 6-12 months if symptoms or findings until age 18
- Renal imaging: every 1-3 yrs, every 6-12 months if findings, usually ultrasound due to cost
- Pulmonary CT in woman at 18 year of age for lymphangioleiomyomatosis (LAM)

SEGA
- Surgical resection
- mTOR inhibitors: rapamycin and everolimus (ClinicalTrials.gov Identifier: NCT01070316; Phase 1/II for epilepsy)

Source: Hallet L 2011; PMID: 21692602.

Incontinentia Pigmenti - Vesicular Stage

Source: www.dermpathmd.com/photos/incontinentia_pigmenti3_la.jpg

Incontinentia Pigmenti


Notes:
Incontinentia Pigmenti cont’d

Incontinentia Pigmenti or IP2
- X-linked dominant Xq28, can have XXY
- NF-κβ essential modulator (NEMO) gene
- Cutaneous
  - Stage 1 vesicular: birth to 2 weeks
  - Stage 2 verrucous: 2-6 weeks
  - Stage 3 hyperpigmentation: 3-6 months
  - Stage 4 hypopigmentation: adult women
- Cataracts, microphthalmos
- Retinal vascular disease
- Microcephaly
- Mental retardation
- Epilepsy
- Hypodontia

Normal Vasculature


Arteriovenous Malformation (AVM)
- <1% of people
- Symptoms due to
  - Mass effect
  - Hemorrhage, often at 15-20 years of age
    - Risk 2%-3% per year
  - Ischemia from shunting of blood flow
- Treatment
  - Embolization
  - Stereotactic radiosurgery
  - Resection

Sturge-Weber

Sturge-Weber cont’d

- Not inherited, sporadic
- Congenital port wine stain
- Leptomeningeal vascular angiomatosis
  - Tram track calcification
- Glaucoma
- Mental retardation

**Ataxia Telangectasia**


- 1/80,000-100,000
- Autosomal recessive, 11q22-23
- Progressive ataxia
  - Chorea and athetosis
  - Distal muscle atrophy, decreased DTR
- Oculocutaneous telangectasia
  - 3-6 years: bulbar conjunctiva and ears
  - Later: flexor surfaces arms, eyelids, malar, chest
- Intellectual deterioration
- Abnormal immunity
  - Cellular: lack T helper cells
  - Humoral immunity: absent IgA and/or IgE, low IgG
  - Recurrent infections
- Elevated alpha fetoprotein (AFP) and carcinoembryonic antigen (CAE)
- Endocrine abnormalities
  - Ovarian agenesis
  - Testicular hypoplasia
  - Insulin resistant diabetes

**Von Hippel-Lindau Disease**

Source: http://www.endotext.org/adrenal/adrenal35/figures/figure1b.jpg

- Autosomal dominant 3p25.3
  - May be modified by 11q13
- Hemangioblastomas of the CNS
  - Retina
  - Brain
- Other tumors
  - Pheochromocytoma: w/o type 1, w/ type 2
  - Clear cell cancer of kidney: w/ 2A, w/o 2B
  - Neuroendocrine tumors of pancreas
- Risk of cancer, esp kidney

Notes:
Hypomelanosis of Ito

Also incontinentia pigmenti achromians or IP1
- Somatic mosaicism, Xp11
- Eye
  - Iris coloboma
  - Cataract
  - Hypertelorism
- Irregular teeth
- Hands: polydactyly or syndactyly
- Epilepsy
- Mental retardation
- Gray matter heterotopia

Notes:

Source: http://imaging.ubmmedica.com/shared/zone5/0809CPRACF4.jpg

Linear Sebaceous Nevus Syndrome

- Up to 1/1000
- Thought to be mosaicism with lethal AD gene
- Hemimegencaphaly
- Mental retardation
- Epilepsy
- Other organs
  - Skeletal abnormalities
  - Ocular abnormalities
  - Cardiovascular
  - Urogenital


Linear Sebaceous Nevus Syndrome with Hemimegencaphaly

Figure 2 MRI of the patient Brain MRI demonstrates the presence of hemimegencaphaly with an enlarged left hemisphere, colpocephaly (A, B), midline shift of a dysplastic occipital lobe (occipital sign, A, B), white matter signal intensity changes (B, C), and straightened frontal horn (arrow, C)

Source: Bindu P S et al. Neurology 2010;74:e27-e27; ©2010 by Lippincott Williams & Wilkins

Linear Sebaceous Nevus Syndrome

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  - Cardiovascular
  - Urogenital

Source: http://jnnp.bmj.com/content/77/7873/F1.large.jpg

Notes:
Klippel-Trenaunay-Weber Syndrome
- 8q22.3, sporadic
- Triad
  - Port wine stain
  - Varicose veins
  - Bony and soft tissue hypertrophy of extremity
    - May have polydactyly or syndactyly
- May have
  - Mental retardation
  - Epilepsy
  - Glaucoma

Answer Key

Question: An in utero ultrasound shows the fetus has holoprosencephaly. There is a family history of both holoprosencephaly and schizencephaly. What is the most likely cause of the fetus’ CNS malformation?
A. CMV infection in utero
B. Environmental toxin
C. Maternal diabetes mellitus
D. Sonic hedgehog mutation
E. Trisomy 13

Question: A 3 y.o. boy comes to clinic with a history of abnormal jerky eye movements, irregular breathing, hypotonia, ataxia, behavior problems and fibrosis of the kidney. His MRI is on the right. What is the most likely diagnosis?
A. Dandy-Walker syndrome
B. Holoprosencephaly
C. Joubert syndrome
D. Lissencephaly
E. Septo-optic dysplasia

Question: Which developmental milestone is a typically developing child expected to acquire LAST?
A. Copy a square
B. Follow a 3-step command
C. Perform a tandem gait
D. Throw overhand
E. Unbutton his/her clothes

Question: A newborn fails the hearing screen and is found to have congenital hearing loss. What else should the child be screened for?
A. Autism
B. Panhypopituitarism
C. Polycystic kidneys
D. Prolonged QT
E. Spina bifida

Notes:
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   D. Tuberous sclerosis
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Notes: