Perinatal & Diseases of infancy and childhood

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<table>
<thead>
<tr>
<th>Terminology</th>
<th>Germinal matrix, intraventricular hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital Anomalies</td>
<td>Fetal hydrops</td>
</tr>
<tr>
<td>Birth weight and gestational age</td>
<td>Inborn errors of metabolism and other genetic disorders</td>
</tr>
<tr>
<td>Birth injuries</td>
<td>Sudden infant death syndrome (SIDS)</td>
</tr>
<tr>
<td>Perinatal infections</td>
<td>Tumors and tumor-like lesions</td>
</tr>
<tr>
<td>Neonatal Respiratory Distress Syndrome</td>
<td></td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td></td>
</tr>
</tbody>
</table>
1. Terminology:

- Embryonic period;
  First 8 weeks of gestational age (GA)
- Fetus;
  9 weeks of GA until birth
- Neonate; age 1-28 days
- Infant; age under 1 year
- Childhood; age 1-14 year
- Premature baby;
  birth weight < 2500 gm. or GA < 37 wks
- Postmature baby;
  GA > 42 wks
- Immature baby;
  birth weight < 1000 gm.
- Term pregnancy;
- Dead fetus in utero;
  เด็กตายในท้อง, detect ได้ก่อนคลอด

- Intrapartum death;
  ตายระหว่างคลอด

- Still birth;
  เด็กคลอดออกมาไม่มี vital signs

- Perinatal death;
  neonatal death + fetal death
<table>
<thead>
<tr>
<th>Causes</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Under 1 Year: All Causes</strong></td>
<td>727.4</td>
</tr>
<tr>
<td>Congenital malformations, deformations, and chromosomal anomalies</td>
<td></td>
</tr>
<tr>
<td>Disorders related to short gestation and low birth weight</td>
<td></td>
</tr>
<tr>
<td>Sudden infant death syndrome (SIDS)</td>
<td></td>
</tr>
<tr>
<td>Newborn affected by maternal complications of pregnancy</td>
<td></td>
</tr>
<tr>
<td>Newborn affected by complications of placenta, cord, and membranes</td>
<td></td>
</tr>
<tr>
<td>Respiratory distress of newborn</td>
<td></td>
</tr>
<tr>
<td>Accidents (unintentional injuries)</td>
<td></td>
</tr>
<tr>
<td>Bacterial sepsis of newborn</td>
<td></td>
</tr>
<tr>
<td>Intrauterine hypoxia and birth asphyxia</td>
<td></td>
</tr>
<tr>
<td>Diseases of the circulatory system</td>
<td></td>
</tr>
</tbody>
</table>
1–4 Years: All Causes

Accidents and adverse effects
Congenital malformations, deformations, and chromosomal abnormalities
Malignant neoplasms
Homicide and legal intervention
Diseases of the heart
Influenza and pneumonia

5–14 Years: All Causes

Accidents and adverse effects
Malignant neoplasms
Homicide and legal intervention
Congenital malformations, deformations, and chromosomal abnormalities
Suicide
Diseases of the heart
2. Congenital Anomalies

- Definition: morphologic defects that are present at birth, but some have clinically apparent until years later (cardiac defects, renal anomalies).

- Major anomaly: anomaly having either cosmetic or functional significance.
Terms used for various kinds of errors in morphogenesis:

- Malformations
- Disruptions
- Deformations
- Sequence
- Syndrome
- Others; agenesis, aplasia, atresia, hypoplasia, hyperplasia, hypertrophy, hypotrophy, dysplasia
Malformations

• Primary errors of morphogenesis
• Intrinsically abnormal developmental process
• Usually multifactorial factors
• May involve single or multiple organ systems
• Such as; congenital heart defects, anencephaly, agenesis of corpus callosum
Anencephaly
Agenesis of corpus callosum
Disruptions

• Result from secondary destruction of an organ or body region that was previously normal in development.
• May be due to either external or internal interferences in morphogenesis
• Classic example; amniotic bands
• Not heritable and not associated with risk of recurrence in subsequent pregnancies.
Deformations

• Pathogenesis; localized or generalized compression of the growing fetus by abnormal biomechanical forces, leading eventually to a variety of structural abnormalities.

• Extrinsic disturbance of development more than intrinsic error
Deformation

• Most common underlying factor; uterine constraint
• Maternal factors; first pregnancy, small uterus, malformed uterus, leiomyomas
• Fetal factors; oligohydramnios, multiple fetuses, abnormal fetal presentation
• Such as; clubfeet, Potter sequence
Club feet
Sequence

• A series of multiple congenital anomalies resulting from a single localized aberration in organogenesis with secondary effects on other organs.

• The primary abnormality may be a malformation, deformation, or disruption.
• Such as;
  renal agenesis or amniotic leakage
  → Oligohydramnios or Potter sequence:
    - flattened facies
    - positional abnormalities of hands and foot
    - lung hypoplasia
    - amnion nodosum
Oligohydramnios

- Renal agenesis
- Amniotic leak
- Others

Fetal compression

- Pulmonary hypoplasia
- Altered facies
- Positioning defects of feet, hands
- Breech presentation

Amnion nodosum
Amnion nodosum; nodules that consist of stratified squamous epithelium.
Potter’s sequence
Syndrome

• Several defects that cannot be readily explained on the basis of a single, localized initiating anomaly.

• Most often caused by a single etiologic agent; viral infection or specific chromosomal abnormality
Agenesis;
   - complete absence of an organ and its associated primordium.

Aplasia;
   - absence of an organ due to failure of the developmental anlage

Atresia;
   - absence of an opening, usually of a hollow visceral organ; trachea, intestine.
Hypoplasia;

- incomplete development or underdevelopment of an organ with decreased numbers of cells.

Hyperplasia;

- overdevelopment of an organ associated with increased numbers of cells
Hypothrophy;
  - decrease in organ size or function related to a decrease in cell size

Hypertrophy;
  - increase in organ size or function related to an increase in cell size

Dysplasia;
  - in context of malformations, describes an abnormal organization of cells
Causes of Congenital anomalies

- Genetic Causes
- Environmental Causes
- Multifactorial Causes
Genetic causes

- Karyotypic abnormalities;
  - 10-15% of live-born infants with congenital abnormalities
  - most cytogenetic aberrations arise as defects in gametogenesis
    * Trisomy 21,
    * Klinefelter syndrome (47,XXY),
    * Turner syndrome (45, XO),
    * Patau syndrome (trisomy 13)
Trisomy 18
(Edward syndrome),
Clench hand
Trisomy 13
(Patau syndrome)
Turner syndrome (45,XO)
• Single gene mutations;
  - relatively uncommon but follow mendelian patterns of inheritance
  - holoprocencephaly, syndactyly, polydactyly
Holoprocencephaly
(Severe alobar form)
Syndactyly
• Multifactorial inheritance;
  - two or more genes of small effect with environmental factors.
  - such as; cleft lip and palate, neural tube defects, and congenital hip dislocation.
Neural tube defect

Spina Bifida  Anencephaly  Encephalocele

Craniorhachichisis
Cleft lip and cleft palate
Environmental causes

• Viruses;
  - *rubella, cytomegalic inclusion disease*, HSV, VZV, influenza, mumps, HIV, enterovirus
  - with all viruses, the GA at which the infection occurs in the mother is critically important.
Rubella:

- The at-risk period for rubella infection extends from shortly before conception to the 16th week of gestation.

- The hazard being greater in the first 8 weeks than in the second 8 weeks.

- The incidence of malformations is reduced from 50% to 20% to 7% if infection occurs in the 1st, 2nd, or 3rd month of gestation.
Rubella embryopathy:

- major tetrad comprises
  - cataracts
  - heart defects (persistent ductus arteriosus, pulmonary artery hypoplasia or stenosis, ventricular septal defect, tetralogy of Fallot)
  - deafness
  - mental retardation
Intrauterine cytomegalovirus infection:

- is the most common fetal viral infection
- the highest at-risk period is the second trimester of pregnancy.
- involvement of the central nervous system is a major feature; mental retardation, microcephaly, deafness, and hepatosplenomegaly
- Drugs and other chemicals:
  - teratogenic agents;
    - thalidomide,
    - folate antagonists,
    - androgenic hormones,
    - alcohol,
    - anticonvulsants,
    - warfarin,
    - 13-cis-retinoic acid
Fetal alcohol syndrome:
- growth retardation
- microcephaly
- atrial septal defect
- short palpebral fissures
- maxillary hypoplasia
• Cigarette smoking;
  - has not been convincingly demonstrated to be a teratogen
  - high incidence of spontaneous abortions, premature labor, placental abnormalities
    - low birth weight, may be prone to sudden infant death syndrome
• Radiation;
  – Radiation is mutagenic, carcinogenic, and teratogenic
  – Exposure to heavy doses during organogenesis can result in such defects as microcephaly, blindness, skull defects and spina bifida
• Maternal diabetes;
  - maternal hyperglycemia-induced fetal hyperinsulinemia causes increased body fat, muscle mass and organomegaly, cardiac anomalies, neural tube defects and other CNS malformations.
3. Birth weight and gestational age

BIRTH WEIGHT
• Appropriate for gestational age (AGA); 10\textsuperscript{th} to 90\textsuperscript{th} percentiles
• Small for gestational age (SGA); below 10\textsuperscript{th} percentiles
• Large for gestational age (LGA); above 90\textsuperscript{th} percentiles
PREMATURITY

• Birth before 37 weeks of gestational age
• Second most common cause of neonatal mortality
• Risk for prematurity
  – 30-40%; Premature rupture of placental membrane (PROM)
  – 25%; Intrauterine infection, chorioamnionitis, funisitis; *Ureaplasma urealyticum, Mycoplasma hominis, Gardnerella vaginalis, Trichomonas, gonorrhea, Chlamydia*

  – Uterine or placental structural abnormalities
  – Multiple gestation (twin pregnancy)
Complication of prematurity

- Hyaline membrane disease (respiratory distress syndrome)
- Necrotizing enterocolitis (NEC)
- Sepsis
- Intraventricular hemorrhage (germinal matrix hemorrhage)
- Developmental delay
Fetal growth restriction (FGR)

- Small for gestational age
- Three main factors:
  1. Fetal
  2. Placental
  3. Maternal (most common)
Fetal:
- chromosomal disorders; trisomy 13, 18, 21
- congenital anomalies
- congenital infections; *TORCH* group
  - toxoplasmosis, rubella,
  - cytomegalovirus, herpesvirus, other
  - viruses or bacteria e.g. syphilis
Placental:
- abruptio placentae
- placenta previa
- placental thrombosis and infarctions
- placental infections
- umbilical-placental vascular anomalies
- multiple gestations
Abruptio placenta
Placenta Previa

Umbilical cord
Placenta in wrong position
Vagina Cervix
Uterus

Placenta in normal position

Prolapsed cord
Maternal:

- underlying mechanism is decreased blood flow to the placenta

- causative factors; toxemia of pregnancy, hypertension, nutritional status, narcotic or alcohol intake, heavy cigarette smoking, drugs
APGAR SCORE:

- A measure of the physiologic condition and responsiveness of the newborn infant
- Evaluated at 1, 5 and 10 minutes
- Predict perinatal morbidity and mortality
- The higher the score, the better the outlook
<table>
<thead>
<tr>
<th>Sign</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A : Appearance</strong> (color)</td>
<td>Blue, pale</td>
<td>Body pink, extremities blue</td>
<td>Completely pink</td>
</tr>
<tr>
<td><strong>P : Pulse</strong> (heart rate)</td>
<td>Absent</td>
<td>&lt;100/min</td>
<td>&gt;100/min</td>
</tr>
<tr>
<td><strong>G : Grimace</strong> (response to catheter in nostril)</td>
<td>No response</td>
<td>Grimace</td>
<td>Cough or sneeze</td>
</tr>
<tr>
<td><strong>A : Activity</strong> (muscle tone)</td>
<td>Limp</td>
<td>Some flexion of extremities</td>
<td>Active motion</td>
</tr>
<tr>
<td><strong>R : Respiration</strong></td>
<td>Absent</td>
<td>Slow, irregular</td>
<td>Good, crying</td>
</tr>
</tbody>
</table>
• 10 → infant in best possible condition
• 5-minute APGAR score
  0-1 → 50% mortality rate
  2-4 → 20% mortality rate
  >7 → 0% mortality rate
4. BIRTH INJURY

**Intracranial hemorrhage**

- Most common important birth injury
- Related excessive molding of head or sudden pressure change
- Predisposing factors
  - Prolonged labor
  - Hypoxia
  - Hemorrhagic disorder
  - Intracranial vascular anomalies
Caput succedaneum & Cephalhematoma

• Caput succedaneum
  – Accumulation of interstitial fluid in the soft tissue of the scalp

• Cephalhematoma
  – Hemorrhage in the subperiosteal tissue
  – 25% associate with skull fracture
Cerebral palsy (CP)

- Cerebral Palsy is caused by damage to the developing brain, usually occurring before, during or shortly after birth.

- Brain damage can also occur during infancy due to infection or trauma.
Perinatal Asphyxia

- Severe hypotensive or hypovolemic event which the fetus suffer, usually around the time of birth
- Disruption of oxygen delivery to the fetus can originate in:
  - Umbilical cord → knot or prolapse of the cord
  - Placenta → abruption
  - Mother systemic circulation → preeclampsia
  - Obstetrical → difficult delivery
True knot
Nuchal cord
• Multiple organ are affected
  1. Widespread marked congestion and hemorrhage
  2. Ischemic necrosis of various organs
5. Perinatal infections

Transcervical (Ascending) infections;
• Cervicovaginal route
• Most bacteria and some virus
  – Herpes simplex virus type II
  – *Escherichia coli*
  – Group B Streptococcus (GBS)
• Chorioamnionitis, funisitis
• Most common sequenlae; pneumonia, sepsis, meningitis
**Group B Streptococcus**

- Most common cause of neonatal sepsis
- Early onset → usually occur within the first few hours after delivery
  - Pneumonia
  - Respiratory distress syndrome
  - Shock
- The mortality averages ~ 50%
- Death: within 24 hours.
• Risk factor to predispose to infection
  – Premature labor
  – Prolonged rupture of membranes
  – Heavy maternal colonization
  – Obstetrical complications

• The presence of group B Streptococci in the mother does not predict severe neonatal infection
• Transplacental (hematologic) infections;
  – Most parasites and viral infections
  – Enter the fetal bloodstream via chorionic villi
  – May occur any time during gestation
  – Sequelae are highly variable, depending on the gestational timing and microorganism
• TORCH infection

T → *Toxoplasma gondii*

O → *Other (Syphilis)*

R → *Rubella virus*

C → *Cytomegalovirus*

H → *Herpes simplex virus type II*

HIV
Multiorgan involvement

- Encephalitis → growth and mental retardation
- Chorioretinitis → cataract and blindness
- Hepatosplenomegaly
- Pneumonitis
- Myocarditis and congenital cardiac defect
- Bone defect
Cytomegalic inclusion disease

• Cytomegalovirus
• Most common transplacental infection
• Multiorgan involvement
  – Intrauterine growth retardation → low birth weight
  – Hepatosplenomegaly
  – Microcephaly → cerebral impairment
6. Neonatal Respiratory Distress Syndrome (RDS)

- Most common cause of respiratory distress in the newborn
- Also known as Hyaline membrane disease
- Formation of membrane in the alveoli
- Almost always occur in preterm
Etiology and pathogenesis:
- occur in the immature lung
- caused by a deficiency of the pulmonary surfactant synthesized by Type II pneumocytes
- Type II pneumocytes are most abundant after 35 wk’s gestation.
- incidence of RDS is 60% in infant GA < 28 wks, < 5% in GA < 37%
• Morphology of lungs;
  – Gross: solid, airless, reddish purple
  – Microscopic: poorly developed alveoli, collapsed alveoli, proteinaceous “membranes” line respiratory bronchioles, alveolar ducts and random alveoli
Respiratory distress syndrome
• Clinical presentation:
  - Typical infant with RDS is preterm with AGA
  - RDS is associated with
    * maternal diabetes (surfactant synthesis is suppressed by high insulin levels)
    * cesarean section delivery

• Assessment of fetal surfactant synthesis:
  - Before delivery: Amniotic fluid phospholipids (lecithin/sphingomyelin ratio)
• Treatment:

Before delivery:
  - Corticosteroids; prevent RDS by inducing formation of surfactant lipids and apoprotein in fetal lung

After delivery:
  – Surfactant replacement
  – Oxygen therapy
• Uncomplicated case; recovery begins in 3 to 4 days

• But infants are risk for developing retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD), both due to high-concentration oxygen therapy

• Other complications of prematurity; patent ductus arteriosus, IVH, NEC
7. Necrotizing Enterocolitis (NEC)

- Spontaneous bowel ischemia
- Clinical features
  - Bloody stool
  - Abdominal distension
  - Absent bowel sound
- Sites: terminal ileum, cecum, and right-sided colon
Abdominal radiographs:
- gas within the intestinal wall
  (pneumatosis intestinalis)

Microscopic: mucosal or transmural
  coagulative necrosis, ulceration, bacterial
  colonization, and submucosal gas
  bubbles.
NEC

• Treatment;
  – Early NEC; conservative treatment
  – 20-60% resection of necrotic bowel segment
Necrotizing Enterocolitis (NEC)
8. Germinal matrix, intraventricular hemorrhage

- Germinal matrix: subependymal tissue
- Severe complication of prematurity
- Typical in less than 32-33 weeks of gestation
- Rare in mature infant
**Clinical features**

- Small hemorrhage → Asymptomatic
- Large hemorrhage → Tense frontanelle → Seizure → Anemia, cyanosis → Apnea
9. Fetal Hydrops

• Generalized edema of the fetus
• Fluid accumulation during intrauterine growth
• Immune and non-immune hydrops
<table>
<thead>
<tr>
<th>TABLE 10–5  Selected Causes of Hydrops Fetalis (in decreasing order of frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
</tr>
<tr>
<td>Malformations</td>
</tr>
<tr>
<td>Tachyarrhythmia</td>
</tr>
<tr>
<td>High-output failure</td>
</tr>
<tr>
<td><strong>Chromosomal</strong></td>
</tr>
<tr>
<td>Turner syndrome</td>
</tr>
<tr>
<td>Trisomy 21, trisomy 18</td>
</tr>
<tr>
<td><strong>Thoracic Causes</strong></td>
</tr>
<tr>
<td>Cystic adenomatoid malformation</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
</tr>
</tbody>
</table>
Fetal Anemia

Homozygous alpha-thalassemia
Parvovirus B19
Immune hydrops (Rh and ABO)

Twin Gestation

Twin-to-twin transfusion

Infection (excluding parvovirus)

Cytomegalovirus
Syphilis
Toxoplasmosis

Major Malformations

Tumors

Metabolic disorders
Hydrops fetalis

• Immune hydrops
  – Hemolytic disease in the newborn caused by blood-group incompatibility between mother and child
  – ABO, Rh blood gr.
• Nonimmune hydrops

*Three major causes*

- Cardiovascular defect
- Chromosomal anomalies; trisomy 18,21
- Fetal anemia unrelated to immune hemolysis

*Homozygous α-thalassemia*

*Most common in SEA*
Twin-twin transfusion syndrome

Left - excessive blood volume

Right - deficient blood volume
Hydrops fetalis
10. Inborn errors of metabolism and other genetic disorders

- Phenylketonuria
- Galactosemia
- Cystic Fibrosis
Phenylketonuria (PKU)

- Dietary phenylalanine;
  - 50% required for protein synthesis
  - Remainder is converted into tyrosine by the *phenylalanine hydroxylase* system

- Mutation of phenylalanine hydroxylase gene >>> variable enzymatic deficiencies
  >>>> elevated phenylalanine
Phenylalanine → Phenylpyruvate (Phenylketone)

Phenylalanine Hydroxylase

Deficient in Phenylketonuria

Tyrosine → Melanins

Multiple Reactions

Fumarate + Acetoacetate
Phenylketonuria

• Classic PKU; Scandinavian
• Clinical features:
  – Normal at birth
  – Rising plasma phenylalanine within the first few weeks of life
  – Impaired brain development and mental retardation
Galactosemia

• Lactose (milk) >>>> glucose + galactose
• Galactose >>>>> glucose; three enzymes
• Autosomal recessive
• Mutation of \textit{galactose-1-phosphate uridyl transferase (GALT)}
• Accumulate galactose-1-phosphate
• Clinical features;
  – Fail to thrive
  – Present with vomiting and diarrhea after milk ingestion
  – Liver – hepatomegaly, cirrhosis
  – Eyes – cataracts
  – Brain – nonspecific alteration; mental retardation
Cystic fibrosis (CF)

- Most common lethal genetic disease affecting whites.
- Affect epithelial chloride ion transport
- Abnormal fluid secretion in exocrine glands and in respiratory, gastrointestinal, and reproductive mucosa
- CF gene; **CFTR (cystic fibrosis transmembrane conductance regulator) protein, cms 7q31.2**
Mutation in cystic fibrosis gene
→ Abnormal gene product
→ 

Impaired cAMP-activated chloride channel
→ 

Impaired chloride and fluid secretion
→ 

Low volume secretions and macromolecular hyperconcentration
→ 

Stasis and obstruction
↓

Pancreas  Intestine  Hepatobiliary  Lungs  Vas deferens
Morphology

- Pancrease; atrophy of exocrine pancreas >>> impaired absorption; avitaminosis A
- Intestine; meconium ileus >>> bowel obstruction
- Liver; diffuse hepatic cirrhosis
- Salivary gland; glandular atrophy
- Male genital tract; azoospermia and infertility
• Lungs; superimposed infection and pulmonary abscess;
  – Three most common organisms:
    *Staphylocooccus areus,*
    *Haemophilus influenzae,*
    *Pseudomonas aeruginosa*
  – *Burkholderia cepacia* is associated with fulminant illness
Cystic Fibrosis

• Clinical course;
  – Malabsorption
  – Cardiorespiratory complications: chronic cough, persistent lung infection, obstructive pulmonary disease, cor pulmonale are the most common cause death
11. Sudden infant death syndrome (SIDS)

- National Institute of Clinical Health and Human Development:
- “sudden death of an infant less than 1 year of age, that remains unexplained after thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history”
SIDS

- Most SIDS deaths occur between 2 and 4 months of life
- Infant usually dies while asleep, without evidence of distress or struggle.
- Pathogenesis; poorly understood, multifactorial disorders
• Potential risk factors;
  – Infant sleeping prone
  – Prematurity and low birth weight
  – SIDS in prior sibling
  – Young maternal age
  – Short intergestational interval
  – Inadequate prenatal care
  – Low socioeconomic status
  – Maternal smoking and drug abuse
12. Tumor and Tumor-like Lesions
TUMOR-LIKE LESION

• Heterotopia (choristoma)
  Normal cells or normal tissue present in abnormal location
  ➔ ectopic pancreas

• Hamartoma
  Focal and excessive over-growth of cells or tissue native to the organ in which it occurs.
BENIGN TUMOR

Hemangioma

• Most common tumor of infancy
• Most are cutaneous; face, scalp
• Flat-to-elevated, irregular, red-blue mass
• Commonly spontaneously regress
Hemangioma
A: Congenital capillary hemangioma

B: Age 2 yrs, after spontaneous regression
Sturge-Weber syndrome
"Port Wine Nevus"
• Lymphangiomas:
  – skin, neck, axilla, mediastinum, retroperitoneum
  – Clinically significant if they encroach on vital structures
  – Histology; cystic and cavernous lymphatic spaces.
Lymphangioma
Teratoma

- Neoplasm made up from different type of tissue
- Most common teratoma of childhood → sacrococcygeal teratoma
- Two peak incidence; age 2 and late adolescence
Sacrococcygeal teratoma
MALIGNANT TUMORS

• Malignant tumors of infancy differs from those of adulthood
  → Incidence and type of tumors
  → Underlying familial or genetic aberration
  → Tendency to regress spontaneously or cytodifferentiate
• Incidence of malignant tumor in children
  1. Leukemia & lymphoma (principally acute lymphoblastic leukemia)
  2. CNS tumors
  3. Neuroblastoma
  4. Sarcoma \(\rightarrow\) rhabdomyosarcoma
  5. Wilm’s tumor
  6. Bone tumors \(\rightarrow\) Ewing sarcoma
  7. Retinoblastoma
Leukemia

• Most common malignancy in children
• Acute lymphoblastic leukemia (ALL) → most common type of leukemia
  – 2-6 years
  – Anemia
  – Thrombocytopenia → petechiae, purpura
  – Hepatomegaly
  – Splenomegaly
  – Lymphadenopathy
Neuroblastoma

• Second most common solid malignancy of childhood (after CNS tumors)
• Most common intra-abdominal solid malignancy in childhood
• 40% arise in adrenal gland
• Remainder → sympathetic chain
• Clinical features
  – Large abdominal mass
  – Metastasis → Bone, lymph node, liver
• 90% of neuroblastoma produce catecholamines
• Elevated blood or urine catecholamine metabolites are important diagnostic features.
• Urine Vanillymandelic acid (VMA); test for pheochromocytoma, ganglioneuroma, neuroblastoma

• Histology:
  - sheets of small round blue cells
  - Homer-Wright pseudorosettes
  - Variable differentiation; schwannian stroma
Suprarenal tumour

Lymph nodes containing metastatic tumour

Neuroblastoma
Wilm’s tumor

• Most common primary renal tumor of childhood; usually age 2-5 yr.
• Second commonest intra-abdominal malignancy of childhood
• Poorly-differentiated renal tumor arising from embryonic metanephric blastema
• Clinical features → abdominal mass
Wilms tumor
• Prognosis:
  – Histologic anaplasia (large cell, hyperchromatic, pleomorphic nuclei and abnormal mitoses); worse prognosis

• Treatment:
  – Chemotherapy; excellent prognosis