Combined Sections Meeting
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DEVELOPMENTAL DELAY IN THE INFANT CANCER PATIENT AND THE ROLE OF PHYSICAL THERAPY

Disclosure

This presenter has no conflict of interest to report regarding any commercial product/manufacturer that may be referenced during this presentation.

Objectives

- To discuss the cancers most often seen during infancy.
- To define developmental delay and how it is determined.
- To understand the causes of developmental delay in infants with cancer.
- To explore the role of physical therapy in the management of developmental delay in this population.

Statistics [1,2]

- Cancer in childhood is RARE
  - 1% of all cancer diagnoses
  - 15,780 estimated cases in 2014
- Occurs less likely during infancy – the first year of life
  - 23:100,000 infants diagnosed annually

Infant Cancers [3,4]

- Different epidemiological, clinical and genetic characteristics than cancers seen in older children
- Diagnostic challenge to identify malignancy
- Treatment decisions must take into account
  - Inherent vulnerability of infants
  - Small size
  - Potential toxicity

Infant Cancers

- Neuroblastoma
- Leukemia
- Brain tumors
- Retinoblastoma
- Wilms tumor

Neuroblastoma [3,5,6]

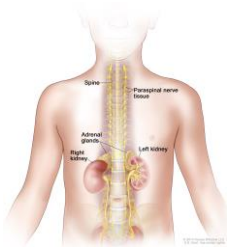
- Neuroblastoma is a cancer of neuroblasts in the sympathetic nervous system
- Represents 6% of all pediatric cancers
  - 700 new cases diagnosed annually
  - 1/3 of all malignancies seen in infants
- Average age of diagnosis is ~1-2 years of age
  - 90% of cases before age 5

Neuroblastoma [3,5,6]

- Risk factors
  - Age, genetic predisposition
- Common locations
  - Adrenal gland
  - Abdominal sympathetic nerve ganglia
  - Spinal sympathetic nerve ganglia (chest, neck, pelvis)

Neuroblastoma [3,5,6]

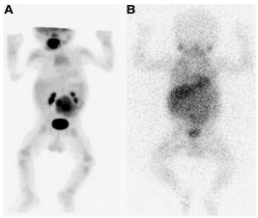
- Symptoms include:
  - Lump/swelling
    - Abdomen
    - Neck
    - Lymph nodes
  - Bone pain
  - Weakness
  - Blueberry muffin sign
  - Opsoclonus-myoclonus



www.cancer.gov

Neuroblastoma [3,5,6]

- Methods of diagnosis
  - Imaging tests
    - Ultrasound
    - CT scan
    - MIBG scan
    - PET scan
  - Laboratory tests
    - Blood
    - Urine catecholamine
  - Biopsy
    - Surgical
    - Bone marrow



jnm.snmjournals.org

Neuroblastoma [5]

Tumor Staging

Stage 1	Stage 2A	Stage 2B	Stage 3	Stage 4	*Stage 4S
• No spread, unilateral tumor involvement, complete surgical removal	• No spread, unilateral tumor involvement, incomplete surgical removal	• Unilateral tumor involvement, complete or incomplete surgical removal, lymph node involvement	• Unilateral or bilateral tumor involvement, complete or incomplete surgical removal, midline tumor involvement,	• Metastatic disease	• <1 year old

Neuroblastoma [5,8]

- Treatment includes:
  - Surgery
    - Tumor resection
  - Chemotherapy
    - Carboplatin
    - Cisplatin
    - Cyclophosphamide
    - Doxorubicin
    - Etoposide
    - Ifosfamide
    - Topotecan
  - Radiation
    - MIBG
  - Immunotherapy
  - Stem cell transplant

Neuroblastoma [5]

- Prognosis

Risk Group	5-Year Survival Rate
Low Risk	95%
Intermediate Risk	90-95%
High Risk	40-50%

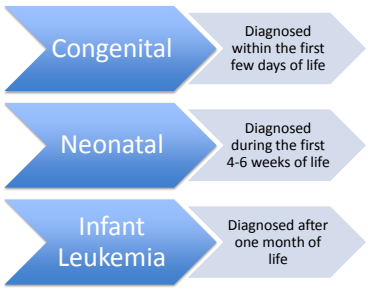
Leukemia [3,9,10]

- Leukemia is a cancer of blood-forming cells
  - Most common cancer seen in children
  - Represents 26% of all pediatric cancers
  - Second most common cancer in infants
- Risk factors
  - Genetic predisposition, radiation, chemotherapy

Leukemia [3,9,10]

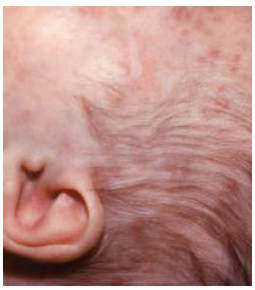
- Types
  - **Acute lymphoblastic leukemia (ALL)**
  - **Acute myelogenous leukemia (AML)**
  - Hybrid/mixed leukemia
  - Juvenile myelogenous leukemia (JMML)
  - Chronic forms of leukemia are uncommon in childhood

Leukemia [3]



Leukemia [3,9,10]

- Symptoms
  - Cutaneous infiltration
  - Fatigue
  - Pallor
  - Easy bruising
  - Weakness
  - Infections



www.visualdx.com

Leukemia [9,10,11]

- Methods of diagnosis
  - Laboratory tests
    - Blood tests (CBC)
  - Biopsy
    - Bone marrow aspiration/biopsy
    - Lumbar puncture

www.fotosearch.com

Leukemia [9,11]

ALL Classification

- Based on immunotype
  - B-cell ALL (80-85%)
    - Early precursor B-cell ALL
    - Common ALL
    - Pre-B ALL
    - Mature B-cell ALL
  - T-cell ALL (15-20%)

Leukemia [9,11]

AML Classification

- Based on morphology
  - M0, M1, M2, M3, M4, M5
    - Starts in immature forms of WBC
  - M6
    - Starts in immature forms of red blood cells
  - M7
    - Starts in immature forms of cells that make platelets

Leukemia [9,12]

- Treatment
  - Chemotherapy
    - Vincristine
    - Daunorubicin
    - Doxorubicin
    - Cytarabine
    - L-asparaginase
    - Etoposide
    - Methotrexate
    - Cyclophosphamide
    - Prednisone
    - Dexamethasone
  - Stem cell transplant
    - High risk disease
    - Relapsed disease
  - Radiation
    - CNS involvement
    - Testicular involvement
    - Pre-SCT

Leukemia [9]

- Prognosis

Leukemia Type	5-Year Survival Rates
ALL	85%
AML	60-70%
JMML	50%

Brain Tumors [3,13,14]

- Brain tumors are abnormal growths in the brain (benign and malignant)
  - Second most common cancer seen in children
    - Most common solid tumor seen in children
  - Represents 19% of all pediatric cancers
  - Third most common cancer seen in infants

Brain Tumors [14]

Histology Classification - WHO

Gliomas
- Astrocytomas
- Oligodendrocytomas
- Ependymomas

Primitive neuroectodermal tumors
- Medulloblastomas
- PNET
- Atypical teratoid rhabdoid tumors

Cranial nerves

Meninges

Brain Tumors [14]

Location Classification - ICCC

Supratentorial
- Four lobes
- Cerebrum
- Ventricle

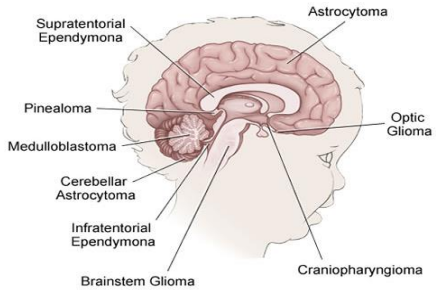
Infratentorial
- Cerebellum
- Brainstem

Gland
- Pituitary
- Pineal

Cranial nerves

Meninges

Brain Tumors



www.acco.org

Brain Tumors [3,13,14]

General Symptoms
- Macrocephaly
- Irritability
- Nausea/Vomiting
- Headache
- Seizures
- Motor weakness

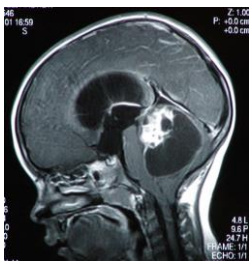
Site Specific Symptoms
- Cerebrum
  - Hemiparesis
  - Sensory loss
  - Speech and memory disturbances
- Posterior fossa
  - Abnormal gait
  - Incoordination
- Brainstem
  - Cranial nerve deficits

Brain Tumors [13,14]

- Risk factors
  - Radiation, genetic predisposition
    - Neurofibromatosis (1, 2), Li-Fraumeni syndrome

Brain Tumors [13]

- Methods of diagnosis
  - Imaging Tests
    - MRI
    - CT scan
  - Biopsy
    - Stereotactic
    - Craniotomy
  - Lumbar puncture



www.chrichmond.org

Brain Tumors [13,16]

- Treatment includes:
  - Surgery
    - Craniotomy
    - Shunt placement
      - Ventriculoperitoneal (VP) shunt
      - External ventricular drain (EVD)
    - Ommaya reservoir
  - Chemotherapy
    - Carboplatin
    - Carmustine
    - Cisplatin
    - Cyclophosphamide
    - Etoposide
    - Lomustine
    - Methotrexate
    - Temozolomide
    - Thiotepa
    - Vincristine
  - Radiation

Brain Tumors [13]

- Prognosis

Tumor Types	5-Year Survival Rates
Pilocytic Astrocytoma	~95%
Fibrillary Astrocytoma	~80-85%
Anaplastic Astrocytoma	~30%
Glioblastoma	~20%
Oligodendroglioma	~90-95%
Ependymoma/Anaplastic Ependymoma	~75%
PNETs (Medulloblastoma, Pineoblastoma	~60-65%

Retinoblastoma [3,17,18]

- Retinoblastoma is a cancer of the eye, starts in the retina
  - Most common eye cancer seen in children
  - Represents 2% of all pediatric cancers
    - 200-300 cases diagnosed annually
  - 11% of cancers diagnosed in the 1st year of life
- Average age of diagnosis is 2

Retinoblastoma [17,18]

- Risk factors
  - Age, genetic predisposition
    - RB1 gene

Retinoblastoma [17,18]

- Types of retinoblastoma
  - Congenital (hereditary)
  - Sporadic
- Can be unilateral, bilateral or trilateral

Retinoblastoma [17,18]

- Symptoms include
  - Leukocoria
  - Strabismus
  - Pain
  - Decreased vision

webeye.ophth.uiowa.edu

Retinoblastoma [3,17,17]

- Methods of diagnosis
  - Imaging tests
    - Ultrasound
    - MRI
  - Ophthalmologic exam

Retinoblastoma [17]

Tumor Staging

Group A	Group B	Group C	Group D	Group E
• 3 mm or less, confined to the retina	• >3 mm or small and close to optic disc or fovea	• Well defined, small subretinal or vitreous seeding	• Large or poorly defined, widespread subretinal or vitreous seeding, possible retinal detachment	• Large, extends forward, bleeding or causing glaucoma

Retinoblastoma [3,17,18]

- Treatment includes:
  - Surgery
    - Enucleation
  - Radiation
    - External beam
    - Brachytherapy
  - Cryotherapy
  - Thermotherapy
  - Photocoagulation
  - Stem cell transplant
  - Chemotherapy
    - Carboplatin
    - Cisplatin
    - Cyclophosphamide
    - Doxorubicin
    - Etoposide
    - Vincristine
    - Topotecan

Retinoblastoma [17]

- Prognosis

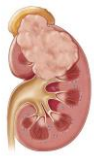
Type	Survival Rate
Overall	94% (5-year)
Metastatic Disease	50%
Trilateral	44% (pineal) 57% (non-pineal)

Wilms Tumor [3,19]

- Wilms tumor is a primary cancer of the kidneys
  - Most common kidney cancer in children
  - Represents 5% of all pediatric cancers
    - 500 cases diagnosed annually
- Average age of diagnosis is ~3-4 years of age
- Risk factors
  - Age, gender, race, genetic predisposition

Wilms Tumor [3,19,20]

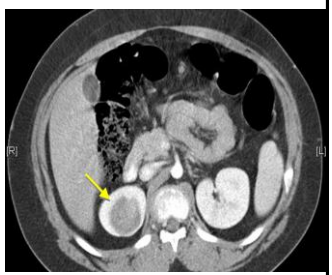
- Types of Wilms tumor
  - Favorable histology
  - Unfavorable histology
- Can be unilateral or bilateral
- Symptoms
  - Abdominal mass/swelling, fever, decreased appetite, nausea



medicalopedia.org

Wilms Tumor [19,20]

- Methods of diagnosis
  - Imaging tests
    - Ultrasound
    - CT scan
    - MRI
  - Biopsy



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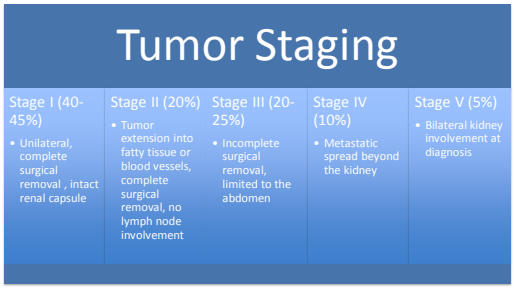
Wilms Tumor [19,21]



Wilms Tumor [19,21]

- Treatment
  - Surgery
    - Radical nephrectomy
    - Partial nephrectomy
  - Radiation
  - Chemotherapy
    - Actinomycin D
    - Vincristine
    - Doxorubicin
    - Cyclophosphamide
    - Etoposide
    - Irinotecan
    - Carboplatin

Wilms Tumor [19,21]

- Prognosis

Tumor Stage	Favorable Histology	Unfavorable Histology
Stage I	99%	83%
Stage II	98%	81%
Stage III	94%	72%
Stage IV	86%	38%
Stage V	87%	55%

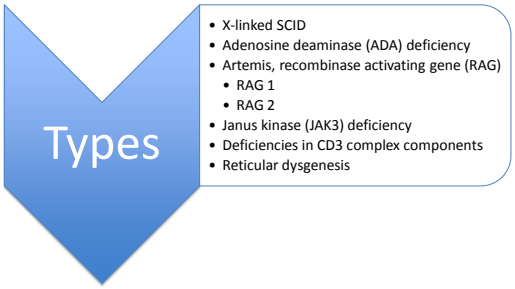
Severe Combined Immunodeficiency (SCID) [22,23]

- Primary immunodeficiency
  - Heterogeneous group of disorders which arise from a disturbance in the development and function of immunity
    - T cells
    - B cells
- "Severe" - lead to early death from significant infections

Severe Combined Immunodeficiency (SCID) [23]

- Statistics
  - 1:50,000-100,000 live births

Severe Combined Immunodeficiency (SCID) [22,23,23]



Severe Combined Immunodeficiency (SCID) [22,23]

- Symptoms
  - Recurrent infections
- Diagnosis
  - Newborn screen
- Treatment
  - Stem cell transplant
  - Enzyme replacement therapy

Developmental Delay

Developmental Delay

- Defined as "a significant delay in the process of development"
- Can occur as a result of various causes
  - Pre-natal
    - Maternal infection
    - Genetic syndromes
  - Peri-natal
    - Difficult childbirth
  - Post-natal
    - Brain injury

Developmental Delay [25]

- Can be seen across several domains/areas of development
  - Physical
    - Gross motor
    - Fine motor
    - Feeding
  - Cognitive
    - Speech
    - Learning
    - Communication

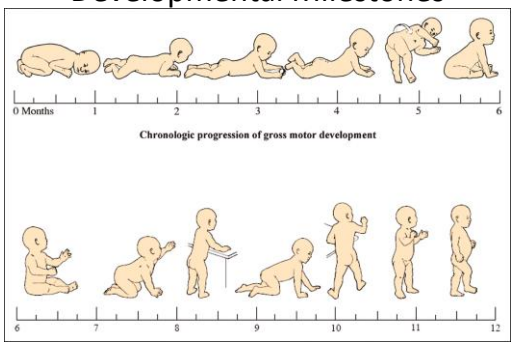
Developmental Areas [25]

Gross Motor	• Use of large muscles
Fine Motor	• Use of small muscles
Speech/Language	• Producing and understanding speech
Cognitive	• Learning and problem solving
Social/Emotional	• Interaction with others, self-control

Developmental Milestones

- A skill that a child achieves within a specific time frame
- Occurs in a sequential fashion
- Can be used as an indication of potential delay

Developmental Milestones



pedsinreview.aappublications.org

Standardized Assessments

- Quantifies amount of delay
- Provides specific information for clinician and parent
- Justifies need for services
- Tracks progress over time

Standardized Assessments

- Alberta Infant Motor Scales (AIMS)
- Peabody Developmental Motor Scale (PDMS)
- Developmental Assessment of Young Children (DAYC)

AIMS

- Norm-referenced test
- Birth to 18 months
- Purpose
  - Identify children with delayed motor development
  - Evaluate motor development/maturation over time

AIMS

Areas of Assessment

- Prone
- Supine
- Sitting
- Standing

PDMS

- Norm-referenced test
- Birth to 5 years old
- Purpose
  - Qualitative and quantitative assessment of fine and gross motor development
  - Recommends activities to address problems

PDMS

Subtests

- Reflexes
- Stationary
- Locomotion
- Object Manipulation
- Grasping
- Visual-Motor

DAYC

- Norm-referenced test
- Birth to 5 years
- Purpose
  - Identify normal and delayed development
  - Determine specific strengths/weaknesses
  - Document progress related to intervention

DAYC

Subtests

- Cognitive
- Communication
- Social-Emotional
- Physical Development
- Adaptive Behavior

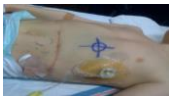
Developmental Delay in Infant Cancers

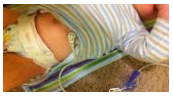
Causes of Developmental Delay in Infant Cancers

- Treatment side effects
  - Chemotherapy
    - Myelosuppresion → decreased energy/activity tolerance, infection
    - Mucositis → impaired oral feeding, impaired weight gain
  - Radiation
    - Fatigue → decreased energy/activity tolerance
  - Surgery
    - Pain → faulty posturing/alignment, impaired reaching/ROM

Causes of Developmental Delay in Infant Cancers

- Line placement
  - Can impede "tummy time" and tolerance of prone positioning, limited UE reaching
    - Central lines
      - Mediport
      - Broviac
    - Feeding tubes
      - PEG/PEG





krissygallagher.worldpress.com www.preemiebabies101.com

Causes of Developmental Delay in Infant Cancers

- Prolonged positioning
  - Impaired alignment
  - Decreased ROM
- Environment
  - Home vs. hospital
    - Limited consistency
    - Impaired sleep/wake cycle
    - Isolation (masks, gloves, gowns)
    - Decreased interaction with peers/social interaction

Role of Physical Therapy

PT Intervention

- Assessment
  - Strength/ROM
  - Muscle tone
  - Alignment
  - Neurological function
  - Resting position
  - Balance
  - Transitions
  - Skill acquisition
  - Play/mobility in supine, prone, sitting, standing

PT Intervention

- Goals
  - Based on current and expected skill level
  - Consider various positions and transitions
  - May require increased time to achieve
  - Involve parents and caregivers

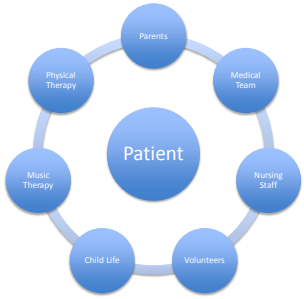
PT Intervention

- Frequency
  - Things to consider
    - Amount of delay
    - Activity tolerance
    - Parental wishes/input
    - Medical treatment needs

PT Intervention

- PT Treatment
  - Strengthening
  - Tolerance of positioning (tummy time, sitting, standing)
  - Balance
  - Gross motor skill acquisition
  - Transitions
  - Ambulation
  - Sensory integration
  - Endurance/cardiopulmonary

Intervention – Team Approach



Intervention – Team Approach

Case Studies

Case Study

- Diagnosed via newborn screen with SCID
- Treatment
  - SCT x 2
- Complications
  - Transplant failure
  - Multiple infections (respiratory, bacterial/viral)
  - Hemolytic anemia requiring multiple transfusions
  - Impaired feeding

Case Study

- Multiple hospital admissions
  - Extended time
  - Consistently on isolation
  - Transfers to PICU for escalated care
- Rehab history
  - Initially evaluated at 3 months
  - Currently receives PT 3x/wk at 2 years old
  - Inpatient, outpatient, early intervention

Case Study

- A few developmental milestones…
  - Head lag, cervical rotation and tilt, hands fisted at 3 months
  - Rolled at 5-6 months
  - Sat independently at 7 months
  - Maintained quadruped at 9 months
  - Showed regression of skills at 11 months
  - Took first independent steps at almost 2 years old

Literature Review [26]

"Physical Functioning in Pediatric Survivors of Childhood Posterior Fossa Brain Tumors" – Piscione, et al

- Cross-sectional assessment of physical functioning using the Bruininks-Osteretsky Test of Motor Performance (BOT-2)
  - Statistically significant differences noted in survivors observed in bilateral coordination, balance and running speed/agility

Literature Review [27]

"Motor Development of Infants with Positional Plagiocephaly" – Kennedy, et al

- Compared the motor development of infants with positional plagiocephaly (PP) and matched peers without using the AIMS and PDMS
  - Young infants placed predominately in the supine position tend to posture their heads preferentially to one side
  - Infants with PP who spent less awake time in prone had lower motor scores

References

1. American Cancer Society. Special Section: Cancer in Children & Adolescents. Available at http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-041787.pdf Accessibility verified 1/3/16
2. St. Baldrick's Foundation. Babies and Cancer. Available at http://www.stbaldricks.org/blog/post/babies-and-cancer-qa?gclid=CL_lg7Z_MkCFQE-nHwodaIIECHg Availability verified 1/3/16
3. Lin, Y. (2003) Early Recognition of Infant Malignancy: The Five Most Common Infant Cancers. *Neonatal Network, 22*, 11-19
4. Orbach, et al. (2013), Neonatal cancer. Lancet Oncology, 14, 609-620
5. American Cancer Society. Neuroblastoma. Available at http://www.cancer.org/cancer/neuroblastoma/detailedguide/index Availability verified 1/3/16
6. Up to Date. Clinical presentation, diagnosis, and staging evaluation of neuroblatoma. Available at http://www.uptodate.com/contents/search?search=neuroblastoma&sp=0&searchType=PLAIN_TEXT&source=USER_INPUT&searchControl=TOP_PULLDOWN&searchOffset=&autoComplete=true_ Availability verified 1/3/16
7. Up to Date. Epidemiology, pathogenesis and pathology of neuroblastoma. Available at http://www.uptodate.com/contents/epidemiology-pathogenesis-and-pathology-of-neuroblastoma?source=search_result&search=neuroblastoma&selectedTitle=3%7E150_ Availability verified 1/3/16
8. Up to Date. Treatment and prognosis of neuroblastoma. Available at http://www.uptodate.com/contents/treatment-and-prognosis-of-neuroblastoma?source=search_result&search=neuroblastoma&selectedTitle=2%7E150 Availability verified 1/3/16
9. American Cancer Society. Childhood Leukemia. Available at http://www.cancer.org/cancer/leukemiainchildren/detailedguide/index Availability verified 1/3/16
10. Up to Date. Overview of the presentation and diagnosis of acute lymphoblastic leukemia in children and adolescents. Available at http://www.uptodate.com/contents/overview-of-the-presentation-and-diagnosis-of-acute-lymphoblastic-leukemia-in-children-and-adolescents?source=search_result&search=acute+lymphoblastic+leukemia&selectedTitle=1%7E150_ Availability verified 1/3/16

References

11. Up to Date. Risk group stratification and prognosis for acute lymphoblastic leukemia in children and adolescents. Available at http://www.uptodate.com/contents/risk-group-stratification-and-prognosis-for-acute-lymphoblastic-leukemia-in-children-and-adolescents?source=search_result&search=acute+lymphoblastic+leukemia&selectedTitle=7%7E150 Availability verified 1/3/16
12. Up to Date. Overview of the treatment of acute lymphoblastic leukemia in children and adolescents. Available at http://www.uptodate.com/contents/overview-of-the-treatment-of-acute-lymphoblastic-leukemia-in-children-and-adolescents?source=search_result&search=acute+lymphoblastic+leukemia&selectedTitle=2%7E150 Availability verified 1/3/16
13. American Cancer Society. Brain and Spinal Cord Tumors in Children. Available at http://www.cancer.org/cancer/braincnstumorsinchildren/detailedguide/index Availability verified 1/3/16
14. Up to Date. Epidemiology of central nervous system tumors in children. Available at http://www.uptodate.com/contents/epidemiology-of-central-nervous-system-tumors-in-children?source=search_result&search=central+nervous+system+tumors+in+children&selectedTitle=3%7E150 Availability verified 1/3/16
15. Up to Date. Clinical manifestations and diagnosis of central nervous system tumors in children. Available at http://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-central-nervous-system-tumors-in-children?source=search_result&search=central+nervous+system+tumors+in+children&selectedTitle=1%7E150 Availability verified 1/3/16
16. Up to Date. Overview of the management of central nervous tumors in children. Available at http://www.uptodate.com/contents/overview-of-the-management-of-central-nervous-system-tumors-in-children?source=search_result&search=central+nervous+system+tumors+in+children&selectedTitle=2%7E150_ Availability verified 1/3/16
17. American Cancer Society. Retinoblastoma. Available at http://www.cancer.org/cancer/retinoblastoma/detailedguide/index Availability verified 1/3/16
18. Up to Date. Overview of retinoblastoma. Available at http://www.uptodate.com/contents/overview-of-retinoblastoma?source=search_result&search=retinoblastoma&selectedTitle=1%7E81 Availability verified 1/3/16
19. American Cancer Society. Wilms Tumor. Available at http://www.cancer.org/cancer/wilmstumor/detailedguide/index Availability verified 1/3/16
20. Up to Date. Presentation, diagnosis, and staging of Wilms tumor. Available at http://www.uptodate.com/contents/presentation-diagnosis-and-staging-of-wilms-tumor?source=search_result&search=wilms&selectedTitle=1%7E86_ Availability verified 1/3/16
21. Up to Date. Treatment and prognosis of Wilms tumor. Available at http://www.uptodate.com/contents/treatment-and-prognosis-of-wilms-tumor?source=search_result&search=wilms&selectedTitle=2%7E86 Availability verified 1/3/16

References

22. Up to Date. Severe combined immunodeficiency (SCID): An overview. Available at http://www.uptodate.com/contents/severe-combined-immunodeficiency-scid-an-overview?source=search_result&search=SCID&selectedTitle=1%7E127_ Availability verified 1/3/16
23. Severe Combined Immunodeficiency. Available at http://www.scid.net Availability verified 1/3/16
24. Up to Date. Severe combined immunodeficiency (SCID): Specific deficits. Available at http://www.uptodate.com/contents/severe-combined-immunodeficiency-scid-specific-defects?source=search_result&search=SCID&selectedTitle=2%7E127_ Availability verified 1/3/16
25. How Kids Develop. Available at http://www.howkidsdevelop.com/developDevDelay.html Availability verified 1/3/16
26. Piscione, PJ., Bouffet, E., Mabbot, DJ., Shams, I., Kulkarni (2014). Physical functioning in pediatric survivors of childhood posterior fossa brain tumors. *Neuro Oncology, 16*, 147-155.
27. Kennedy, E., Majnemer, A., Farmer, JP., Barr, RG., Platt, RW (2009). Motor development of infants with positional plagiocephaly. *Physical and Occupational Therapy in Pediatrics, 29*, 222-235