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# Recognizing subtle signs and symptoms of pediatric cancer

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CANCER IS A RARE occurrence in children and adolescents, accounting for 1% of all newly diagnosed cancers in the United States. However, it's the leading cause of disease-related deaths among children ages 1 to 19 in the United States.<sup>1-3</sup> A cancer diagnosis evokes much fear and anxiety in parents and caregivers, but early diagnosis and treatment can result in improved patient outcomes.

Nurses are often the first healthcare professional to identify the signs and symptoms of cancer. They can help parents most by suggesting that the child be seen by the primary care provider or pediatric oncologist for a complete evaluation. This article reviews the presenting signs and symptoms of the most common types of childhood cancers.

## **Inside the statistics**

The annual incidence of all types of pediatric cancers is estimated to be 186.6 per 1 million of those up to age 19, representing a slight increase over the past 30 years.<sup>4</sup> This translates to about 15,780 newly diagnosed cases of cancer in children and adolescents in 2014, with an estimated 1,960 deaths annually in the United States.<sup>3</sup>

Despite the slight increase in incidence, the mortality from pediatric cancer has declined by 66% over the past 30 years, from a 5-year survival rate of less than 50% to approximately 83% today.<sup>3</sup> Hispanic and non-Hispanic White children have the highest rates of childhood

and adolescent cancer and non-Hispanic Black children have the lowest rates.<sup>4</sup> Children from lower socioeconomic status (SES) households have a disproportionately higher rate of death from cancer compared with those from households with higher SES.<sup>1,3</sup> The incidence and mortality of childhood cancer is higher in boys than girls.<sup>4</sup>

### Causes and risks

Although the definitive etiology of childhood cancer is still largely unknown, certain risk factors may predispose children to developing cancer. These fall into three major risk categories: genetic, environmental, and microbial. (See *What are the risk factors for pediatric cancers?*) Specific infectious agents such as HIV may be a risk factor; research to support this is ongoing.<sup>3</sup> However, most childhood malignancies result from alterations in DNA and acquired mutations.<sup>1,3,5</sup>

### Clinical manifestations

Early signs and symptoms of childhood cancers can be nonspecific, and they often mimic those of other disorders. General signs and symptoms can be summarized with the mnemonic CHILD CANCER. (See *Signs and symptoms of pediatric cancer.*) This

tool can help pediatric healthcare providers and parents recognize possible signs and symptoms early and initiate further assessment and treatment appropriate for the specific cancer.

In order of prevalence, the most common malignancies in children from birth to age 14 years are acute lymphoblastic leukemia, central nervous system (CNS) tumors, lymphoma, neuroblastoma, Wilms tumor, acute myeloid leukemia, bone tumors, rhabdomyosarcoma, and retinoblastoma. Hodgkin lymphoma is the most common malignancy in adolescents ages 15 to 19.<sup>1</sup>

### Acute leukemia

Accounting for about one-third of all childhood cancers, acute leukemia is the most common type of pediatric cancer. Acute lymphoblastic leukemia (ALL) accounts for 75% of leukemias in children, followed by acute myeloid leukemia (AML) and other chronic types of leukemia including chronic myelogenous leukemia (CML) and juvenile myelomonocytic leukemia.<sup>1</sup> ALL usually occurs in early childhood with peak incidence between ages 2 and 4 years.<sup>1</sup>

This disease arises in the bone marrow. Risk factors specific to leukemia include ionizing radiation, immunosuppressant drugs

(including chemotherapy), and genetic factors such as trisomy 21 (Down syndrome) and Fanconi anemia.<sup>1,6</sup>

The many possible presenting signs and symptoms of leukemia are related to the overproduction of immature white blood cells (WBCs), which decreases the ability of the bone marrow to produce other mature cell lines.<sup>3</sup> Classic signs and symptoms of leukemia include the following.

- **Anemia.** The patient's history may include fatigue, inability to keep up with peers, frequent resting while playing or during activities, dizziness, shortness of breath, tachycardia, or palpitations.

- **Thrombocytopenia.** The patient may present with easy bruising and bleeding, petechiae, hematuria, or a history of epistaxes.

- **Pallor.** Pale skin and conjunctivae develop secondary to anemia.

- **Fever.** Often of unknown origin or without a source, fevers can recur due to WBC suppression.

- **Recurrent infections.** Open infected lesions or infections that don't improve on antibiotics can occur.

- **Bone or joint pain.** About 20% of patients with leukemia have this presenting symptom.<sup>1</sup>

Nonspecific presenting signs and symptoms include malaise,

## What are the risk factors for pediatric cancers?<sup>1,6</sup>

### Genetic risks

- immunodeficiencies, such as Fanconi anemia
- chromosomal abnormalities, such as trisomy
- inherited gene mutations
- genetic syndromes, such as Bloom syndrome, neurofibromatosis

### Environmental risks

- ionizing radiation
- solar radiation
- drugs (such as immunosuppressants, diethylstilbestrol)
- low maternal vitamin intake
- certain types of chemotherapy, including alkylating agents and topoisomerase II inhibitors
- parental exposure to chemicals, solvents, or pesticides

### Microbial risks

- hepatitis B virus
- human papillomavirus
- HIV
- *Helicobacter pylori*
- Epstein-Barr virus

anorexia, cough, headaches, vomiting, seizures, hepatomegaly, and splenomegaly.<sup>1</sup>

Any suspicious findings should be promptly investigated with diagnostic studies or referral to a pediatric oncologist. Initial lab studies include a complete blood cell (CBC) count with platelet count, which may reveal a high, low, or normal WBC count, neutropenia, anemia, and thrombocytopenia.<sup>1</sup> A definitive diagnosis of leukemia is made on the basis of a bone marrow biopsy that shows immature blood cells (blasts).

Treatment for acute leukemias in children includes chemotherapy, radiation, and possibly bone marrow or stem cell transplant. The 5-year survival rate for ALL is around 85%, for AML, from 60% to 70%, and for CML, from 60% to 80%.<sup>1</sup>

### CNS cancers

Malignant brain and spinal cord tumors represent the second most frequent type of childhood cancers in children from birth to age 14, accounting for 21% of all childhood cancers.<sup>1,7</sup> Diagnosis peaks at ages 2 to 10.

Approximately 26% of malignant CNS tumors in children occur in the cerebellum and brainstem, and 17% are located in the frontal, parietal, temporal, and occipital lobes. Tumors arising in the cerebrum and ventricles account for about 12% of CNS tumors. The remaining tumors occur in the meninges, cranial nerves, spinal cord, and cauda equina.<sup>7</sup> Types of brain tumors and their incidence include the following:

- gliomas, approximately 52%. These include glioblastoma, astrocytoma, oligodendroglioma, ependymoma, brainstem glioma, and optic glioma.
- primitive neuroectodermal tumor, often known by the acronym PNET, 20%.<sup>1</sup>

## Signs and symptoms of pediatric cancer

Use the mnemonic CHILD CANCER as a quick assessment tool.

- **C**ontinued, unexplained weight loss
- **H**eadaches, often with early-morning vomiting
- **I**ncreased swelling or persistent pain in bones, joints, back, or legs
- **L**ump or mass, especially in the abdomen, neck, chest, pelvis, or armpits
- **D**evelopment of excessive bruising, bleeding, or rash
- **C**onstant infections
- **A** whitish color behind the pupil
- **N**ausea that persists or vomiting without nausea
- **C**onstant tiredness or noticeable paleness
- **E**ye or vision changes that occur suddenly and persist
- **R**ecurrent or persistent fevers of unknown origin.

Source: Feist P. Signs of childhood cancer. Pediatric Oncology Resource Center. <http://www.ped-onc.org/diseases/SOCC.html>.

The cause of brain and spinal cord tumors in children and adolescents is still largely unknown. However, exposure to ionizing radiation and genetic or inherited disorders such as tuberous sclerosis, neurofibromatosis types 1 and 2, von Hippel-Lindau disease, and Li-Fraumeni syndrome are associated with an increased risk of developing CNS tumors.<sup>1</sup>

Presenting signs and symptoms of brain and other CNS cancers depend on the child's age. Infants and young children whose fontanels haven't yet closed may have virtually no detectable signs or symptoms of a brain tumor except for an increasing head circumference, which occurs because the skull expands as the tumor grows. This is one reason why accurately measuring and documenting head circumference until patients reach age 2 and palpating the fontanels is important. Children in this age group may express discomfort through head rolling and fussiness. (See *Sorting out the signs and symptoms of brain tumors by age.*)

Imaging studies such as computed tomography (CT) or magnetic

resonance imaging (MRI) are used to identify brain and spinal cord tumors. A definitive diagnosis of the type of CNS tumor requires a biopsy. Brain and other CNS tumors are treated with surgery (if the tumor is operable), chemotherapy, and radiation. For children up to age 19, the survival rate for brain and other CNS cancers ranges from approximately 95% for pilocytic astrocytoma to 60% to 65% for PNET.<sup>1</sup>

### Lymphoma

Affecting the lymphoid tissues, lymphomas are the third most common cancer in children and adolescents. The two broad categories of lymphoma, non-Hodgkin lymphoma and Hodgkin lymphoma, account for 5% and 4% of childhood cancers, respectively. Non-Hodgkin lymphomas occur most frequently in younger children, while Hodgkin lymphomas develop more frequently in adolescents. Non-Hodgkin lymphoma is also more common in boys than girls.<sup>1</sup>

Risk factors associated with non-Hodgkin lymphoma include exposure to radiation, congenital immune deficiency syndromes such



as Wiskott-Aldrich syndrome, common variable immunodeficiency, ataxia-telangiectasia, severe combined immunodeficiency syndrome, Bloom syndrome, and X-linked lymphoproliferative syndrome. Other risk factors include HIV and Epstein-Barr virus (EBV). Risk factors for Hodgkin lymphoma include EBV infection, male gender, HIV infection, having a sibling with Hodgkin lymphoma, and higher SES status.<sup>1</sup>

The most common presenting sign of lymphoma is painless lymphadenopathy, especially in the supraclavicular and axillary areas. These nodes are typically firm and rubbery. A persistent, painless supraclavicular lymphadenopathy should raise a red flag for the practitioner.<sup>1</sup>

### Sorting out the signs and symptoms of brain tumors by age

In infants and children under age 2 years:

- bulging fontanels secondary to the buildup of cerebrospinal fluid and increased intracranial pressure (ICP)
- vomiting secondary to increased ICP
- irritability
- poor feeding.

In children over age 2, presenting signs and symptoms result from increased ICP:

- morning headaches that improve throughout the day
- headaches that cause waking
- vomiting without nausea and unrelated to meals
- blurred vision or diplopia
- dizziness
- gait disturbances or ataxia, including tripping or falling a lot or walking into things
- personality or behavioral change
- seizures
- nystagmus.

Source: American Cancer Society, 2014.

Patients with mediastinal masses, which are also common in those with non-Hodgkin lymphoma, present with a persistent unexplained cough. Other common presenting signs and symptoms include malaise, fever, weight loss, pain, night sweats, and pruritus.<sup>1</sup>

A diagnostic workup for lymphoma includes a biopsy, lumbar puncture, bone marrow aspiration and biopsy, a CBC count, chest X-ray, ultrasonography, CT, and/or MRI.<sup>1</sup>

Both Hodgkin and non-Hodgkin lymphoma are treated with chemotherapy, monoclonal antibodies, and stem cell transplant. Radiation therapy is used more frequently in treating Hodgkin lymphoma. The overall 5-year survival rate for non-Hodgkin lymphoma exceeds 85%. The 5-year survival rate for Hodgkin lymphoma ranges from about 65% for stage IV to about 90% for stage I.<sup>1</sup>

### Neuroblastoma

This autonomic nervous system cancer represents 6% of all childhood cancers. Neuroblastoma is found only in children, usually in those younger than 5 years; the average age at diagnosis is 2 years.<sup>1</sup>

Neuroblastoma begins in the neuroblasts of the sympathetic nervous system. In young children, immature nerve cells are scattered throughout the body, so tumors associated with this cancer can be found anywhere in the body. Typical locations are the abdomen, neck, chest, pelvis, and spinal cord.

Although signs and symptoms of neuroblastoma vary depending on where the tumor arises, most patients present with an abdominal mass.<sup>1,8</sup> Besides a palpable mass in the abdomen, pelvis, or neck, presenting signs and symptoms of neuroblastoma may include abdominal pain, constipation, proptosis, periorbital ecchymoses, bladder

dysfunction, hypertension, anemia, bone pain, fever, and weight loss.<sup>1</sup>

Because neuroblastoma is associated with increased levels of circulating catecholamines, urine and blood specimens are obtained for vanillylmandelic acid (VMA) and homovanillic acid (HVA). Other diagnostic studies include biopsy, CT, MRI, ultrasonography, and a metaiodobenzylguanidine (MIBG) scan. This scan uses MIBG (a chemical similar to norepinephrine) that has a small amount of radioactive iodine. An MIBG scan is specific for neuroblastoma.<sup>1</sup>

Treatment includes surgery, radiation, chemotherapy, immunotherapy, retinoid therapy, and stem cell transplant.<sup>1</sup> About 50% to 60% of children with neuroblastoma present with metastatic disease because the signs and symptoms don't begin until after the disease has progressed.<sup>9</sup> The overall 5-year survival rate ranges from approximately 40% to 50% for children in the high-risk group to greater than 95% for children in the low-risk category.<sup>1</sup>

### Wilms tumor (nephroblastoma)

This kidney cancer is the most common intra-abdominal tumor of childhood. Wilms tumor makes up 5% of all childhood cancers, typically in children under age 5. The incidence of Wilms tumor is slightly higher in girls and in Black children.<sup>1</sup>

Risk factors for Wilms tumor include having a family history of Wilms tumor, genetic disorders such as WAGR (Wilms tumor, aniridia [completely or partially missing iris], genitourinary tract abnormalities, and mental retardation), and Denys-Drash and Beckwith-Wiedemann syndromes. Children with other defects such

as aniridia, cryptorchidism (undescended testes), hypospadias, and hemihypertrophy (one arm or leg that's larger than the other) also have a higher risk of Wilms tumor.<sup>1</sup>

Wilms tumor can grow quite large before being found. Typically it presents as a unilateral painless abdominal mass, unless it's grown large enough to compress other abdominal organs.<sup>10</sup> Often parents are the first to find an enlarged abdominal mass when they bathe or lift the child because children this young typically have very little fat or muscle surrounding their kidneys. Other presenting signs and symptoms of Wilms tumor may include increased abdominal girth, abdominal pain, malaise, hypertension, and microscopic hematuria.<sup>1</sup>

Children with risk factors for Wilms tumor should have a screening abdominal ultrasound every 3 or 4 months up until age 8.<sup>1</sup> Diagnostic workup for Wilms tumor includes ultrasound, CT or MRI, chest X-ray, bone scan, urinalysis, and a kidney biopsy.

Treatment for Wilms tumor includes surgery, chemotherapy, and, in some patients, radiation. The overall 4-year survival rates for Wilms tumor range from 87% for stage V with favorable pathology (55% for unfavorable pathology) to 99% for stage I with favorable pathology (83% for unfavorable pathology).<sup>1</sup>

### **Rhabdomyosarcoma**

This soft-tissue cancer of the striated muscle can occur anywhere in the body, but it's typically found in the head, neck, extremities, and genitourinary tract.<sup>11</sup> Three percent of childhood malignancies are rhabdomyosarcomas.<sup>1</sup>

The main types of rhabdomyosarcoma are embryonal, the most common type, which usually affects younger children, and alveolar



**Long-term follow-up is an important part of care for survivors of pediatric cancers.**

rhabdomyosarcoma, which usually affects older children and teens. Genetic disorders such as Li-Fraumeni syndrome, neurofibromatosis type I, Beckwith-Wiedemann syndrome, and Costello syndromes are associated with an increased risk for developing rhabdomyosarcoma.<sup>1</sup>

The signs and symptoms of rhabdomyosarcoma can vary, depending on where this cancer originates. For instance, if the mass arises in the nasal cavity, signs and symptoms may appear earlier because this body cavity is very small. Although an abdominal mass can cause vomiting and constipation or a palpable mass, sometimes no early signs or symptoms can be detected.

A mass and pain may be presenting signs and symptoms wherever this tumor arises. If the tumor arises in the orbital area, findings may

include proptosis and ophthalmoplegia (oculomotor paralysis). If the tumor arises near the nose, patients may experience nasal obstruction, epistaxis, and sinusitis. Patients may also present with facial nerve palsy, palpable cervical lymph nodes, and chronic serous otitis media if the tumor is in the head, neck, or facial area. A palpable or visible mass may also be present.<sup>1</sup>

Diagnostic workup for rhabdomyosarcoma includes X-rays, CT or MRI, positron emission tomography (PET), bone scan, ultrasonography, biopsy, bone marrow aspiration and biopsy, lumbar puncture, and a CBC count.<sup>1</sup>

Treatment for rhabdomyosarcoma includes surgery, chemotherapy, and radiation. The 5-year survival rates for rhabdomyosarcoma are 90% for children in the low-risk group, 60% to 80% for children in the intermediate-risk group, and 20% to 40% for children in the high-risk group.<sup>1,3</sup>

### **Retinoblastoma**

Retinoblastoma, a rare cancer that arises from the retina, accounts for 3% of all childhood cancers. Retinoblastoma occurs in about 200 to 300 children annually, usually in children younger than age 5. This type of cancer is either heritable (about 30% of cases) due to an abnormality in the *RBI* gene or non-heritable (about 70% of cases).<sup>1</sup> Patients with heritable retinoblastoma have a positive family history of the disease. These patients should have early screening, such as fundoscopic examination under anesthesia.<sup>3</sup>

The most common presenting sign of this type of tumor is leukocoria; this abnormal white pupillary reflex is also known as *cat's eye reflex*.<sup>12</sup> Less common findings include strabismus, a red eye, and nystagmus.<sup>1</sup>

Treatment includes enucleation with orbital implant, chemotherapy, radiation therapy, laser photoablation, brachytherapy, and cryotherapy. The overall 5-year survival rate for retinoblastoma is approximately 99%.<sup>1</sup>

### **Osteosarcoma**

This aggressive bone cancer comprises less than 2% of childhood cancers, but it's the most common primary bone tumor affecting children.<sup>1</sup> Osteosarcoma is most frequently seen in teens and affects the large bones of the arms or legs, and most often occurs near the metaphyseal growth plates of the long bones.<sup>3</sup> About 42% of these tumors occur in the femur, but they can also occur in the tibia, humerus, skull, jaw, and pelvis.<sup>13</sup>

Children with Paget disease, fibrous dysplasia, enchondromatosis, Rothmund-Thomson syndrome, Bloom syndrome, Werner syndrome, Diamond-Blackfan anemia, and Li-Fraumeni syndrome are at increased risk for developing osteosarcoma.<sup>1,3</sup> Other risk factors for osteosarcoma include male gender, Black race, exposure to radiation, and having hereditary retinoblastoma.<sup>1</sup>

### **Watch out for long-term problems<sup>1</sup>**

Long-term effects of childhood cancer and treatment include problems in these areas:

- growth and development
- cognition
- vision
- hearing
- behavior
- cardiovascular system
- musculoskeletal system
- pulmonary system
- teeth
- reproductive system.

Many adolescents who play organized sports complain of joint and leg pain from overuse, which may delay the diagnosis. Assessing for this type of tumor in the distal femur is important if pain thought to be related to sports activity isn't relieved by rest.

General signs and symptoms of this type of cancer are localized pain, which may be worse at night or with activity, and a soft tissue mass, which is frequently large and tender to palpation.<sup>1</sup> Limping is a common sign if the tumor is in the lower extremities. If the tumor is found on the upper extremities, presenting signs and symptoms may be decreased strength and dexterity. The adolescent may also drop things being carried.<sup>3</sup>

Diagnostic workup for osteosarcoma includes X-ray, CT or MRI, bone scan, PET, serum alkaline phosphatase, and serum lactate dehydrogenase.<sup>1</sup>

Treatments for osteosarcoma include limb-salvage surgery, amputation, chemotherapy, and in certain cases, radiation therapy. The 5-year survival rate for localized disease is 60% to 80% and for metastatic disease, 15% to 30%.<sup>1</sup>

### **Implications for nursing practice**

The early signs and symptoms of childhood cancers can be fairly vague and often mimic common childhood illnesses, which may consequently delay diagnosis and treatment. The diagnostic interval (DI) is the time between presentation of signs and symptoms and the diagnosis of cancer. A recent study examining the factors associated with the length of the DI for childhood cancer found that children ages 5 to 9 were more likely to have a longer DI compared with all children up to age 14. Practitioners recognized "alarming" signs and symptoms in

19% of presenting cases. Children with leukemia had the shortest DI if their presenting signs and symptoms included fatigue, anemia, or ecchymoses, while those with bone and CNS tumors had the longest DI. Overall, fatigue was associated with a shorter DI in all types of pediatric cancers; in patients with leukemia, pain was associated with a longer DI. Vomiting was the only sign that was associated with a shorter DI in patients with brain tumors.

Parents are often the first to notice that something isn't right with their children and bring them to their primary care providers for further evaluation. Providers and nurses need to be vigilant about investigating any suspicious signs and symptoms and encouraging parents to keep their appointments for routine well-child visits. Nurses in well-child offices, school-based clinics, and other pediatric settings can also elicit key information by asking focused questions while obtaining a health history and performing a physical assessment.

An appropriate diagnostic evaluation is important when childhood cancer is suspected. The nurse can be instrumental in helping parents obtain appropriate care for a child who needs further assessment, shortening the DI and improving patient outcomes. For a high suspicion of a childhood cancer or an abnormal finding suggesting cancer, the nurse should encourage prompt referral to the primary care provider, pediatric ED, and a pediatric oncologist who's a member of a multidisciplinary team and part of the Children's Oncology Group.<sup>1</sup>

The diagnosis of cancer should be communicated to parents by the pediatric oncologist or primary care provider. The nurse can then offer them critically needed support and

keep them informed about the diagnosis and treatment.

### Long road ahead

Despite the fact that mortality has declined, childhood cancer continues to be a devastating diagnosis. Children with cancer and their families are affected not only by the disease and treatments, but also by significant effects on the child's physical and emotional development. Long-term follow-up is an important part of care for survivors of pediatric cancers. (See *Watch out for long-term problems.*)

Resources available to nurses, providers, and parents can be found at the American Childhood Cancer Organization (<http://www.acco.org>), National Cancer Institute (<http://www.cancer.gov>), Starlight Children's Foundation (<http://www.starlight.org>), and the American Cancer Society (<http://www.cancer.org>). ■

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