

Cancer in the pediatric patient

When to suspect it?

When to be alarmed?

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Abstract

Childhood cancer frequently presents in a non-specific manner, simulating other benign diseases. This fact, associated with its low incidence, hinders the suspicion and diagnosis of childhood cancer. Early diagnosis and prompt referral to a specialized center significantly reduce morbidity and mortality, improving the prognosis of the disease. There are many signs and symptoms that should alarm the physician and even family members, which are: pallor, long-lasting fever, headache, lymphadenopathy, bleeding, or bruising, marked weakness, masses, abnormal gait, ocular abnormalities, skeletal muscle pain, among others. Although these are usually nonspecific, it is important to detect early warning signs and red flags to improve survival in the pediatric population with this condition. Based on the literature, the aim of this review article is to characterize the clinical manifestations in the pediatric patient that suggest a prompt intervention and search for a neoplasm in the child.

Key words: neoplasm, childhood cancer, signs and symptoms, alarm.

Search methodology

A literature search was performed from February 1 to March 31, 2022, in PUBMED, GOOGLE SCHOLAR, MEDLINE, UPTODE with the terms MESH "Neoplasms", "Childhood cancer", "Signs and symptoms", "Alarm". The inclusion criteria were articles dealing with childhood cancer, its symptoms and alarm signs as a central theme, as well as books, journal articles, reviews

and case reports published in the last 20 years in English and Spanish; resulting in an initial 40 articles. Those related to cancer in adults were excluded. Those duplicated or with insufficient or irrelevant content to develop the topic were not taken into account. Finally, 35 publications were obtained, of which 22 were considered to be in accordance with the objective of the present study.

Resumen

El cáncer infantil se presenta frecuentemente de forma inespecífica, simulando otras enfermedades de curso benigno. Este hecho, asociado a su baja incidencia, dificulta la sospecha y el diagnóstico de cáncer infantil. Si se hace este último de manera precoz junto con la rápida derivación a un centro especializado, se reducen significativamente la morbilidad y la mortalidad, lo que favorece el pronóstico de la enfermedad. Existen muchos signos y síntomas que deben alarmar al médico e incluso a los familiares: palidez, fiebre de larga duración, dolor de cabeza, adenopatías, sangrados o moretones, debilidad marcada, masas, marcha anormal, anormalidades oculares, dolor músculo esquelético, entre otros. Aunque estos tienden a ser inespecíficos, es importante detectar oportunamente los signos de alarma y bandera roja para mejorar la supervivencia en la población pediátrica con esta condición. Con base en la literatura, el objetivo de este artículo de revisión es caracterizar las manifestaciones clínicas en el paciente pediátrico que sugieren una rápida intervención y búsqueda de una neoplasia en él.

Palabras clave: neoplasias, cáncer infantil, signos y síntomas, alarma.

Metodología de búsqueda

Se realizó una búsqueda en la literatura desde el 1 de febrero hasta el 31 de marzo de 2022, en PUBMED, GOOGLE SCHOLAR, MEDLINE, UPTODE con los términos MESH “Neoplasias”, “Cáncer infantil”, “Signos y síntomas”, “Alarma”. Los criterios de inclusión fueron artículos que trataran como tema central el cáncer infantil, sus síntomas y signos de alarma, así mismo, se incluyeron libros, artículos de revista, revisiones de tema y reportes de caso publicados en los últimos 20 años en inglés y español; obteniéndose inicialmente 40 artículos. Se excluyeron los relacionados a cáncer en adultos. Aquellos duplicados o con contenido insuficiente o no relevante para desarrollar el tema, tampoco fueron tenidos en cuenta. Finalmente, resultaron 35 publicaciones, de las cuales 22 fueron considerados acordes al objetivo del presente estudio

1. Introduction

Childhood cancer is defined as any tumor, neoplasm or condition that favors abnormal cell growth in tissue and can appear at any time during childhood or adolescence¹. Although its incidence is low, it is still the second leading cause of death in developed countries¹. Cancer is often not so easy to diagnose in the first instance, as the symptoms and signs are nonspecific and often mimic benign and much more common diseases². The most frequent types in childhood are acute leukemias, brain tumors, lymphomas, and solid tumors such as Wilms tumor and neuroblastoma^{1,3}, among others. There are different risk factors for developing cancer such as exposure to certain pesticides, smoking or alcohol during pregnancy and infection by certain viral microorganisms such as Epstein Bar Virus (hereinafter EBV), human immunodeficiency virus (hereinafter HIV), hepatitis B and C and others⁴. It should also be noted that some genetic diseases have a higher risk of developing cancer⁵, such as Down syndrome, which has a substantially higher risk of developing acute leukemia⁶. Beyond recognizing the groups or risk factors predisposed to cancer, it is essential to identify in a timely manner the clinical manifestations that suggest malignancy (red flags) in order to raise the suspicion of a neoplasm and rapidly initiate the search and exploration of the same, since this has a favorable impact on childhood morbidity and mortality due to cancer⁷. The main objective of this article is to characterize semiology of the most relevant clinical manifestations that suggest an active search and rapid intervention of a neoplasm/malignancy in pediatric patients.

2. Epidemiology

Childhood cancer continues to be an important cause of mortality in this population and the most common cause of death in children aged 1 to 15 years⁸. In developed and high-income countries, it is a leading cause of death in children and adolescents^{1,9}. Worldwide, it is estimated that approximately 300,000 to 400,000 cancers are diagnosed each year in children under 19 years of age and about 80,000 children die from this disease each year worldwide^{1,9}. These figures may be higher, as 80% of pediatric cancer occurs in low- and middle-income countries, where there are no or limited childhood cancer registries. Mortality is higher in boys compared to girls and higher in adolescents than in younger children². In Colombia there are about 2,200 children with cancer, more than half of these cases correspond to leukemias, central nervous system tumors and lymphomas. Mortality

lity due to cancer in the country has remained stable, with 4.13 deaths per 100,000 minor inhabitants in the year 2020¹⁰. For the metropolitan area of Bucaramanga, leukemias represent 39% of all neoplasms with an overall annual rate of 52.6 cases per million in males¹¹, results obtained in the only population-based registry of childhood cancer published in the capital of Santander. Table 1 summarizes the most frequent types of cancer (in all age groups); however, it should be noted that the frequency of certain tumors is higher in some age groups compared to others; for example, leukemia occurs more frequently in children under 10 years of age².

Table 1. Most frequent malignant neoplasms in infants, children and adolescents.

Type of cancer	Percentage
Leukemias	27
Central nervous system tumors	15
Lymphomas	16
Germ cell tumors	8
Soft tissue sarcoma	6
Thyroid cancer	6
Bone tumors	5
Neuroblastoma	4
Wilms tumor	4
Retinoblastoma	2

3. Warning signs and symptoms - red flags

As mentioned, cancer in children can start with symptoms that suggest a benign course, even so, there are symptoms and signs that suggest malignancy^{12,13,14}. This symptomatology has been defined as red flags or alarm signs, which, combined with an adequate clinical history and physical examination, should alert the physician, and generate a high suspicion of cancer¹². The following list summarizes these clinical manifestations, followed by a clear and concise description of the most important ones.

- Unexplained pallor and significant loss of energy.
- Masses or lumps. For example, palpable abdominal mass.
- Unexplained weight loss.
- Prolonged fever that does not go away.
- Bleeding or bruising.
- Continuous and prolonged pain in one or more areas of the body.
- Lameness or gait disturbance.

- Frequent headaches associated with vomiting.
- Sudden changes in the eyes or vision or blindness.

The importance of these manifestations lies in the fact that at least 85% of children or adolescents with cancer initially present some of these signs or symptoms¹⁴ and that the remaining 10-15% debut with unusual presentations, which makes diagnosis and suspicion of a neoplasm even more difficult. However, the clinical semiology of cancer is complex, and these symptoms/signs of alarm are not exclusive of malignancy, but they should alert the health professional to look for a possible case¹⁴. The following is a brief description of the clinical manifestations and features that should alarm the physician to initiate the investigation of a neoplasm in the pediatric patient:

3.1. Fever

Temperature higher than 38 degrees that is permanent or prolonged (more than two weeks)^{2,12}, which is not attributed to an infectious cause on physical examination. However, fever is still the most common cause of an infectious condition and only approximately 6% of cases of prolonged febrile syndrome without focus correspond to neoplasm¹⁵. It is usually associated with other alarming symptoms such as weight loss, night sweats, hemorrhagic manifestations, bone pain or lymphadenopathy¹².

3.2. Weight loss

Any child who starts with marked anorexia associated with unexplained (more than 10% in the last 6 months) unintentional weight loss¹². Suspicion of cancer should be raised when the patient presents with pallor, bruising, bone pain or constitutional symptoms (fever or night sweats)¹⁴.

3.3. Pallor and fatigue

Lack of energy and mucocutaneous pallor usually appear in non-malignant causes. However, they should be alarming if they are persistent or associated with signs of bone marrow infiltration (fever, recurrent infections, hemorrhagic manifestations) and/or lymphadenopathy^{2,8,12}.

3.4. Headache

New onset headache, usually in the morning or waking the child during sleep and associated with vomiting or neurological manifestations (motor signs, cranial nerve palsies or sensory deficits)¹². Pay attention to occipital headache or if it worsens with Valsalva maneuvers or is associated with behavioral changes¹². Patients presenting with such symptomatology should undergo neuroimaging as soon as possible, as favorable results have been demonstrated when there is a decrease in the time to diagnosis and perfor-

mance of the imaging test¹⁶. The diagnostic image of choice is MRI and if this is not possible, a CT scan should be performed¹⁷.

3.4. Lymphadenopathy

It is defined as an enlargement of the lymph nodes which are palpable on physical examination. This finding is common in children and does not always indicate malignancy, since the most common cause is infectious^{2,12}. A neoplasm should be suspected when the lymph node is clearly enlarged (according to its location, see Table 2) and is persistent over time (4 to 6 weeks)^{2,8,18}. Table 2 summarizes the characteristics that should alarm the physician to study such lymphadenopathy, either with a blood test or a biopsy (if required).

Table 2. Clinical features of malignant lymphadenopathy.

	Consistency	Size	Location	Associated symptoms
Lymphadenopathy suspicious of malignancy	Firm, hard, adherent, rubbery. Not painful	<ul style="list-style-type: none"> - Cervical and axillary: more than 1 centimeter (cm). - Inguinal: more than 1.5 cm. - Epitrochlear: more than 0.5 cm 	Supraclavicular or epitrochlear	Fever, night sweats, weight loss, pallor, hepatosplenomegaly B or constitutional symptoms

3.5. Bone or joint pain

About 20% of children newly diagnosed with acute lymphoblastic leukemia present with skeletal muscle pain¹⁹. If it is of recent onset, persistent and intense, it should always alarm the physician. Suspicion of malignancy is increased when it lasts more than 2 weeks, wakes the child at night and is associated with local inflammatory signs that do not improve with non-steroidal anti-inflammatory drugs^{2,12}. Likewise, functional limitation, a painful hip in a child under 3 years of age or the inability to walk², are findings that should be of concern to the physician, and should lead to the search for a neoplasm. For this reason, anamnesis and physical examination are valuable tools when a child with osteoarticular pain comes to the physician's office.

3.5. Ocular symptoms

There are multiple ocular symptoms that should be studied immediately, even in the newborn. Timely fundus examination and evaluation of the retinal red reflex helps to exclude and suspect retinal cancer in a timely manner²⁰. The following symptoms or clinical findings require immediate specialized attention and evaluation¹²:

- Squinting, diplopia, or strabismus: red flag for eye or central nervous system tumor¹².
- Leukocoria (white pupillary reflex, Figure 1): red flag for retinal tumor. Approximately 20-60% of children with neuroblastoma debut with this finding²⁰.
- Proptosis: red flag for space-occupying lesions of orbit¹².



Figure 1. Photograph of an 18-month-old boy with leukocoria of the left eye.

Diagnosis: Left retinoblastoma.

Source: Kaufman et al. ²¹.

4. Conclusions

Childhood cancer has an extensive list of clinical manifestations that are usually non-specific and in most cases are similar to clinical conditions with a better prognosis, which proves to be a diagnostic challenge for the physician or pediatrician. It is necessary and of utmost importance to perform an adequate anamnesis, listen to parents and caregivers and perform a complete and detailed physical examination. Early diagnosis of childhood cancer requires a high index of suspicion on the part of the physician, who must know the risk groups and timely and accurately identify red flag signs and symptoms, which accelerates the process of diagnosis, referral, and timely treatment in a specialized pediatric oncology center. These strategies have a positive impact on the prognosis of the disease^{1,12,13}, not only by reducing morbidity and mortality, but also by improving the quality of life of the child and their family²².

5. Conflict of interest

The authors declare that there is no conflict of interest.

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