

Childhood cancer: Early warning signs

Early diagnosis improves prognosis.

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World-wide there are more than 200 000 new cases of childhood cancer per year and more than 70% of these occur in the developing world. In the First World more than 70% of these children will become long-term survivors. For some childhood cancers 5-year survival rates approach 95%. In England only 0.5% of all cancer cases occur in children under 15 years of age. In Third World countries this ratio is often higher, and in India the percentage in some areas is almost 5%. Despite these higher incidences it is often not a health priority in developing countries, where other health needs are more important. In the USA, even though cancer is rare in children, it is the fourth most common cause of death in under 19-year-olds, it is also more common in males, and adolescents have a higher death rate than children. In India the most common malignancies in children are leukaemia, with an incidence of between 25% and 40%, followed by lymphoma and then central nervous system tumours. In South Africa figures for 2008 reveal a leukaemia incidence of about 22%, followed by an equal incidence of CNS and lymphomas (15% each) and the fourth most common malignancy is nephroblastoma with an incidence of 10% (SACCSG data base).

Why do we need to make the diagnosis early?

If patients are diagnosed early the prognosis is improved. Patients with stage 1 or 2 disease have a better prognosis than those with stage 3 or 4 disease. The survival rates in the First World are much better than in South Africa because more patients present and are diagnosed early. Our patients present late because they seek medical help late and our medical staff are often not aware that cancer can occur in children. On occasions inappropriate medical interventions are performed, further delaying the diagnosis. The diagnostic workup for and the initial management of childhood cancer should be under the auspices of a paediatric oncologist and preferably in a paediatric oncology centre with all the necessary sub-specialties available to fully and rapidly evaluate the child.

How do we make an early diagnosis?

This rests on three key issues: a high index of suspicion, recognising high-risk groups and recognising the 'red flags'.

High index of suspicion

In general practice cancers are rare, and unless you think of the diagnosis, it is going to be missed. The common sites to be aware of include blood and bone marrow, brain, bone, lymph nodes and abdominal tumours as well as soft tissues. In children with these systems involved a malignancy should always be considered.

Recognising high-risk groups

There are certain specific circumstances where one must be especially vigilant about the possibility of a malignancy:

- Children with neurocutaneous syndromes, who are prone to both benign and malignant tumours.
- Children with chromosomal disorders including Down syndrome, Fanconi's anaemia and other chromosomal break syndromes.
- Children with immunodeficiency states, whether they are acquired or inherited. These children are especially prone to lymphomas and their enlarged glands need to be evaluated appropriately.
- Children who are higher risk for other reasons. This includes children with a history of a previous malignancy (due to the chemotherapy drugs used as well as the use of radiotherapy). Children whose siblings have had a malignancy, including twins, also need to be evaluated carefully. Children who have cirrhosis, from whatever cause, also need to be monitored for development of liver cancers.
- Children with congenital malformations and syndromes are also prone to develop malignancies, including children with Beckwith-Wiedman syndrome. Children with aniridia (absent iris) (Fig. 1) and hemi-hypertrophy should also be closely followed up.

Recognising the 'red flag signs' of childhood cancer (Table I)

At least 85% of paediatric cancers are associated with this group of signs and symptoms. The remaining 10 - 15% present with unusual

Table I. SACCSG/CHOC red flag signs of cancer*

S	Seek medical help early for persistent signs
I	'Eye' signs such as white spot in pupil, squint, blindness or bulging eye
L	Lumps in abdomen, pelvis, head and neck region, limbs, testes and lymph nodes
U	Unexplained fever, LOW, LOA, pallor, fatigue, easy bruising and bleeding
A	Aching bones, joints, backache, easy fractures
N	Neurological: change in behaviour, balance or gait problems, loss of milestones, headache and increasing head circumference

*Use of the mnemonic St SILUAN to remember the red flag signs for childhood cancers.



Fig. 1. Aniridia.

signs or symptoms and are difficult to diagnose. These signs and symptoms are not exclusive for malignancies but should alert the general practitioner to the possibility of a malignancy.

Pallor or purpura

These are worrying signs in children, especially if they occur together. There are many causes for anaemia and in malignant disease it is usually caused by bone marrow infiltration by abnormal cells (leukaemia, neuroblastoma and lymphoma) and may be due to excessive bleeding from the low platelet count that often accompanies bone marrow infiltration. Investigation of patients with anaemia and purpura (Fig. 2) often reveals multiple abnormalities on the full blood count. Bleeding is usually from the nose or persistent oozing from the gums but also includes skin bleeds. On occasions more catastrophic bleeds may occur, including intracranial bleeds. Any patient who has pallor and bleeding must have a full blood count performed to evaluate the haemoglobin, white cell count and platelet count. The most common diseases affecting the bone marrow are leukaemia, lymphoma and neuroblastoma.



Fig. 2. Bruises associated with leukaemia.

Bone and joint pain

This is an uncommon symptom in childhood cancers but it may be the presenting sign of both primary and secondary bone tumours. Bone pain that wakes children at night, occurs persistently in one area or is associated with loss of function, refusal to walk or other physical

signs such as swelling, tenderness or redness must be further investigated and malignancies must be considered. In 20 - 30% of patients with leukaemia bone pain (Fig. 3) may be the presenting symptom, while up to 60% may have musculoskeletal symptoms or signs. Backache in children must be taken seriously as children seldom complain of it unless there is a reason, so that full evaluation for the possible cause must be undertaken. Spinal and vertebral tumours and bone infiltrations may all present with backache. Many tumours spread to the bone and can cause bone pain, including retinoblastoma, histiocytosis, rhabdomyosarcoma and neuroblastoma.



Fig. 3. Bone changes with acute leukaemia.

For some childhood cancers 5-year survival rates approach 95%.

Lymphadenopathy

This is a common complaint and finding in children. Children usually have small cervical and axillary nodes some time during their childhood due to their exposure to various viruses and bacteria. The size varies, but in general a node is considered to be enlarged if it is greater than 1 cm but the epitrochlear node >0.5 cm and inguinal node >1.5 cm are accepted exceptions. Most causes of lymphadenopathy are benign and related to infections and inflammation. They may be the presenting sign/symptom of leukaemia, lymphoma, histiocytosis or neuroblastoma as well as germ cell tumours (Fig. 4). It is uncommon in soft tissue and bone tumours. The incidence of a malignancy in lymph node biopsies is higher when there are constitutional symptoms (i.e. fever, night sweats or weight loss); the nodes are firm, rubbery, matted and non-tender, and occur in the supraclavicular, postauricular or epitrochlear areas. Abdominal and mediastinal nodes are worrying, but although they are most often due to tuberculosis in South Africa, lymphomas and other malignancies must be excluded. Nodes associated with pallor, purpura, hepatosplenomegaly or other masses must be fully evaluated and a malignancy excluded. Lymph node biopsies should



Fig. 4. Massive lymph nodes from a T-cell lymphoma.

be considered when the FBC shows unexplained abnormalities, there are large mediastinal or abdominal nodes that are not easily explained, the nodes are associated with constitutional symptoms, the nodes increase or fail to decrease in size despite 2 - 4 weeks' appropriate treatment, or if nodes are asymptomatic and >2.5 cm in size.

Unexplained masses

Any unexplained mass in any area of the body may be the first clinical sign or symptom of a malignancy. Masses occur in any area of the body and the site is often a clue to the possible cause of the mass. These masses may be groups of lymph nodes (see above) or the mass may arise from other organs in the body. Masses in the abdomen can be from any of the intra-abdominal organs but the most common are renal masses (nephroblastoma, neuroblastoma). However, hepatic, ovarian or bladder masses and an enlarged spleen are also worrisome in children. These masses often present as an incidental finding by the caregiver although abdominal pain, vomiting, constipation and even intestinal obstruction may occur on occasions. Matted abdominal nodes may also present as a central mass that would need further evaluation. Testicular masses can also be due to a variety of malignancies including leukaemia, rhabdomyosarcoma and germ cell tumours. Head and neck masses (usually lymph nodes) can also be due to a variety of malignancies such as lymphoma, rhabdomyosarcoma and leukaemia. Mediastinal masses (Fig. 5) are always worrisome in children and although a large number will be due to tuberculosis, lymphomas, leukaemia, germ cell tumours and neuroblastoma may all present asymptotically or with coughing, shortness of breath, hoarseness and stridor.

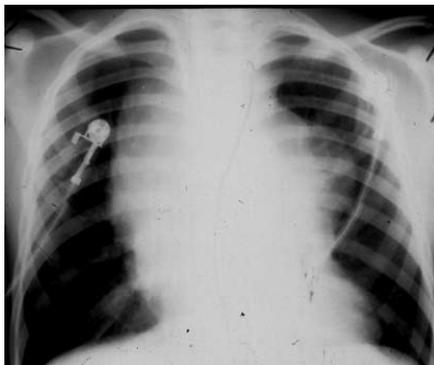


Fig. 5. Mediastinal mass.

Unexplained neurological symptoms and signs

These signs and symptoms are those essentially associated with raised intracranial pressure (Fig. 6). Headaches, although fairly common in children, are rarely caused by intracranial tumours. Any headache that is present for more than 2 weeks, is associated with early morning vomiting or co-ordination difficulties, needs to be further evaluated as a matter of urgency. Sudden onset of squints, ataxia and changes in behaviour may all be signs and symptoms of serious intracranial disease. Loss of milestones, enlarging head circumference associated with splaying of the sutures, sunset eye sign and prominent veins on the head may all be signs of raised intracranial pressure. These children need urgent and rapid evaluation by means of CT or MRI scans.



Fig. 6. Raised intracranial pressure.

Changes in the orbit or eye

Loss of vision and development of a squint are all-important changes that may be indicative of an underlying malignant process. Any child over 3 months who develops a squint should be evaluated for a possible retinoblastoma; early detection may result in an extremely good outcome. The presence of a white pupil is also

of concern and may be due to cataract or an underlying retinoblastoma and needs to be further evaluated (Fig. 7). Proptosis can be an early sign or symptom of orbital pathology that includes neuroblastoma, retinoblastoma, rhabdomyosarcoma, lymphoma and leukaemia, as well as a number of benign lesions. This obviously needs further urgent evaluation.



Fig. 7. Normal red reflex, leukocoria in the left eye due to retinoblastoma.

Persistent and unexplained fever and weight loss

Fever is a common complaint in children, and although it is often due to infection, a fever that does not respond to routine treatment should arouse suspicion of a malignancy. Only between 2% and 9% of prolonged fevers are due to a malignant process. Lymphoma is the classic malignancy that causes prolonged fever, often associated with loss of weight and night sweats. In South Africa tuberculosis is the most common cause of this triad of symptoms but lymphoma must be remembered if there are other unexplained clinical signs. Urinary tract infections, HIV and tuberculosis as well as autoimmune diseases also need to be considered in these patients and should be excluded. These patients may need invasive investigations to arrive at a diagnosis.

What do you do when you have diagnosed a malignancy or strongly suspect it?

Who should you refer?

ALL children or adolescents under the age of 15 years with a suspected malignancy should be referred.

Who do you refer to?

Refer the patient to a paediatric oncology centre or paediatric oncologist. Any child under the age of 15 years should be discussed and referred to a paediatric oncologist if possible. If the unit feels the patient is too big or too old they will advise to whom the patient should be referred.

Where do you find paediatric oncologists?

- There is a unit at each teaching hospital complex.
- There are a limited number of paediatric oncologists in full-time private practice.
- There are a limited number of state-employed paediatric oncologists in private practice.

What should you do before referral?

- Discuss with a paediatric oncologist before referral.
- Try to avoid referral directly to surgical disciplines.
- Try to avoid doing invasive procedures as they often have to be repeated or are inappropriate.
- Make sure the patient is stable and able to travel.

Further reading

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In a nutshell

Despite a relatively high incidence of paediatric cancers in the developing world these are generally not a health priority in these areas.

If patients are diagnosed early the prognosis is improved. Patients with stage 1 or 2 disease have a better prognosis than those with stage 3 or 4 disease.

Patients in the developing world often present and are diagnosed late.

In general practice cancers are rare and unless you think of the diagnosis it is going to be missed.

The common sites to be aware of include blood and bone marrow, brain, bone, lymph nodes and abdominal tumours as well as soft tissues.

Early diagnosis requires: a high index of suspicion, recognising high-risk groups and recognising the red flag signs of childhood cancer.

Refer ALL children under the age of 15 in whom you suspect a malignancy.

There are a limited number of paediatric oncologists in private practice, so the child often has to go to a state hospital or teaching hospital with a paediatric oncology unit.