Malignant Solid Tumours In Children: A Clinical Appraisal

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INTRODUCTION

Lymphomas are the commonest childhood malignant solid tumours in the tropics. Of theses series Burkitt's lymphoma is by far the most common. [1,2,3] Other important malignant solid tumours even though of less prevalence when compared to Burkitt's lymphoma are retinoblastoma, nephroblastoma, rhabdomyosarcoma, osteogenic sarcoma, neuroblastoma, CNS malignancies, germ cell/ gonadal tumors, hepatoblastomas and hepatocellular carcinomas.

The discussion here will be limited to 5 of these malignancies- retinoblastoma, nephrobalstomas, rhabdomyosarcomas, osteogenic sarcoma and neuroblastoma.

1. RETINOBLASTOMA

It is the commonest ocular malignancy arising from precursor cells of rods and cones in the posterior portion of the retina.[4]

In 60% of cases- unilateral and hereditary; 15% of cases unilateral and hereditary; 25% of cases bilateral and hereditary.[5]

It is commonly seen in the 1st 5 years of life.

Clinical features

1. Leukocoria/ Cat eye's reflex (white papillary reflex) is usually the first noticeable sign seen in 60% of cases.
2. Progressive loss of vision
3. Squints may be the first complaint in some cases
4. Eye pain/ discharge
5. Proptosis/ fumigating orbital mass.
6. Pan opthalmitis
7. Hyphaema
8. Vitreous haemorrhages

Investigations

1. Orbital radiographs which may show intra-tumoral calcification in 75% of cases
2. Ultrasonography to evaluate intraocular and extra-ocular spread.
3. Computed tomography (CT) scan also to evaluate intraocular extent and extraocular spread
4. Complete blood count

The following investigations may also be necessary if indicated by either clinical, laboratory or imaging findings.

5. Cerebrospinal fluid examination
6. Skeletal survey
7. Carcinoembryonic antigen (CEA) which is usually increased
8. Alpha-feto proteins, also usually increased
9. Radionuclide bone scans of the head
10. Bone marrow sampling

Diagnosis should be confirmed by binocular indirect opthalmoscopy with sclera depression under general anaesthesia.

Treatment

1. Enucleation for the unilateral disease. Small tumors can be treated with photocoagulation or cryotherapy with careful follow up for evidence of recurrences [5].
2. For the bilateral disease chemotherapy and radiationwith/without surgical enucleation of the worst eye. Drug of choice include combination of Cyclophosphamide and Vincristine or Cytosan and Adriamycin.[4]

Differential diagnosis of Leukokoria [6].

1. Retinoblastoma
2. Congenital cataract
3. Toxocara canis
4. Persistent hyperplastic primary vitreous
5 Coat's disease
6. Large chorioretina coloboma

7. Retina dysplasia
8. medulloepithelioma (diktyoma)
9. Congenital retinal fold
10. Retinopathy of prematurity

2. NEPHROBLASTOMA(Wilm's Tumour)
It was first described in 1899 by the German surgeon, Max Wilms [7] .It is an embryonal tumour that develops within the kidney parenchyma is usually associated with congenital anomalies. Such as Genitouriary anomalies (in 4.4%), hemihypertrophy (2.9%), sporadic aniridia (1.1%) [4,8]. Two rare syndromes associated with WT are:
- WAGR syndrome constituted by Wilm's tumour, aniridia, genitourinary anomaly and mental retardation.
- Denys-Drash Syndrome constituted by Wilm's tumour, nephropathy and genital abnormalities [8].

The peak incidence of unilateral WT is about 3 years [8].

Clinical features
1. Abdominal or flank mass:
- often unilateral , asymptomatic , smooth and firm
- it occurs more on the right than on the left [9].
- mass rarely crosses the midline and grows along the vertical axis
- bilateral kidney involvement in about 5-10% of cases [8].

2. Abdominal pain with/without vomiting
3. Haematuria either gross or microscopic in 10-25% of cases [8].
4. Hypertension in about 60% of patient. It can be due to:
- renal ischaemia due to pressure on renal artery
- ectopic rennin or ACTH production by the tumour [8,10].
5. Weight loss
6. Polycythaemia due to erythropoietin production .It is a rare paraneoplastic syndrome [8].
7. Bone pain
8. hypercalcaemia due to prostaglandins or parathormone secretion by the tumour [1].

Investigations
1. Plain abdominal x-ray shows soft tissue opacity displacing the gut in the area normally occupied by the kidney.
2. Abdominal ultrasound- which may show intrarenal mass
3. C.T Scan - to confirm intrarenal tumour origin
- to determine the extent of the tumour including vena cava involvement
- rules out other tumours e.g neuroblastoma.

4. Intravenous urethrogram (IVU) shows dilatation and elongation of the calices (spider-leg deformity) [9].
5. Chest X-ray which in 10-15% of cases show evidence of pulmonary metastasis at the time of diagnosis [8].
6. Renal function test
7. Urinalysis (for microscopic haematuria)
8. Bone marrow sampling
9. Liver function tests
10. Complete blood count and other baseline investigations.

Treatment
1. For unilateral involvement:
- Surgery with chemotherapy; if the tumour is completely respectable.
- Surgery with chemotherapy and irradiation in cases of local extension

2. For stage IV: combination chemotherapy with radiotherapy
3. For stage V: perioperative chemotherapy to shrink the tumour with surgery (Heminephrectomy) on one side and radical nephrectomy on the more involved contra lateral side.

The chemotherapy combination commonly used is
Actinomycin D 15□g/kg I.V daily for 5 days ,then at 6 weeks + Vincristine 1.5mg/m^2 (maximum dose is 2mg) I.V once weekly for 6 weeks, then repeat every 3 monthly for 2 years.
Adriamycin may be added to the combination at a dose of 60mg/m^2 per day at 6 weeks, then repeat 3 monthly. [1,11]

3. NEUROBLASTOMA
A malignant tumour of neural crest origin with a peak incidence in the first 3 years of life and is rarely seen after 6 years of age. Common locations of neuroblastoma are the adrenal medulla, cervical, thoracic and the pelvic ganglia. Rarely, ectopic forms arise in the kidney [10].
Early metastasis constitutes the hallmark of the disease [4].

Clinical features
Neuroblastoma is characterized by protean manifestations some of which are:
1. Abdominal mass:
- 50% of which is of suprarenal origin [13].
- Hard fixed and irregular
- crosses the midline
- displaces the kidney downward and outward
- usually nontender

2. Abdominal pain may be present
3. Fever
4. Bone pain due to marrow infiltration
5. Easy fatigability
6. Anaemia which is normochromic normocytic in 70% of cases [13].
7. Weight loss
8. Hepatosplenomegaly
9. Focal neurological signs due to either intraspinal disease or cord compression

10. Anorexia
11. Dyspnoea from compression on the airway by an intrathoracic mass
12. Paroxysmal hypertension from catecholamine release with/without renal vascular compression
13. Secretory diarrhea due to production of other vasoactive substances
14. Orbital ecchymoses/proptosis due to orbital deposits
15. Opsoclonus- myoclonus a.k.a "Dancing eyes dancing feet" syndrome [12] which is a rare paraneoplastic syndrome of the disease and it manifests as chaotic eye movements , myoclonus and ataxia.
16. Subcutaneous nodules in bone metastases
17. Horner's syndrome from cervical ganglion involvement.

Infants commonly have the disease restricted to the cervical or thoracic region while older children usually have abdominal neuroblastomas and disseminated disease [12].

Investigations
1. Plain abdominal x-ray shows calcified abdominal mass and/or widened paraspinal shadow
2. CT scan is best for confirming abdominal tumours and intraspinal extension
3. Serum Catecholamine levels is elevated in 70-90% of patients [13]
4. Urine examination for tumour markers or catecholamine metabolites such as:
- homovanillic acid (HVA) and Vanillylmandelic acid (VMA) levels are raised in 85% of patients
- dopamine level is increased in 90% of patients.
-about 10% are metabolite negative [10].

5. Radionuclide bone scan using technetium or meta-iodobenzylguanidine (MIBG)
6. Bone marrow study by aspiration and biopsy to show neuroblasts which may simulate leukaemic cells in marrow involvement.
7. Magnetic Resonance Imaging (MRI) can also demonstrate marrow disease
8. Liver Function tests
9. Renal Function tests
10. Chest x-ray
11. Peripheral lymph node biopsy
12. Complete blood count

Treatment
It is based on the International Neuroblastoma Staging System:
Stages I & II - Surgery
Stage III - preoperative Chemotherapy and Surgery
Stage IV - Chemotherapy with surgery and radiotherapy

Drug regimens used include -
1. I.V Vincristine 1.5mg/m^2 stat on Day 1, with I.V cyclophosphamide 1g/m^2 stat on Day 1 and I.V Darcarbazine 250 mg/m^2 on Days 1- 5. These should be repeated every 3 weeks for 6-12 months [11,13].
2. Cyclophosphamide with Doxorubicin [4]
3. VM26 with Cisplatinum and Epipodophylotoxin. [4]

4. RHABDOMYOSARCOMA

This is the commonest soft tissue sarcoma in children. It has an early peak before 5 years and a late peak in adolescence. In the first peak, common sites involved are the head, neck, prostate, urinary bladder and vagina while in the second peak genitourinary and extremities are the major sites. The retroperitoneum could also be affected [4].

Clinical features
They normally depend on the site affected but the most common feature is a mass with/without pain in the affected region.
1. Head and Neck:
- nasal congestion, epistaxis, mouth breathing, swallowing difficulties, croupy cough, stridor, ptosis, proptosis, periorbital oedema, decreased visual acuity, cranial nerves palsy , features of elevated Intracranial pressure, ear pain, hearing loss, chronic otorrhoea.
2. Genitourinary system:
- pelvic/suprapubic mass, haematuria, a rapidly growing scrotal mass, bladder outlet obstruction, recurrent UTIs, incontinence, grape-like vaginal mass (Sarcoma botryoides), vaginal bleeding.
3. Extremities:
Usually manifests as a rapidly growing painless mass.
Symptomatic hypercalcaemia is a feature of extensive bone involvement.

Investigations
1. X-ray of the affected site
2. Ultrasonography to determine abdominal and pelvic involvement
3. CT Scan to confirm the extent of the organ and bone involvement
4. Cystourethrogram for bladder tumours
5. Radionuclide scans
6. Chest X-ray to rule out pulmonary metastases
7. Tumour biopsy for confirmation
8. Bone marrow sampling
9. Renal function tests
10. Serum chemistry
11. Complete blood count

Treatment

It is based on the International Rhabdomyosarcoma Staging (IRS):
Group I tumours - Surgery with Chemotherapy
Group II and III - Surgery with chemotherapy and local irradiation
Group IV Chemotherapy.

Drug regimen commonly used is: Vincristine 1.5mg/m^2 I.V on Day 1 with Actinomycin D 1.5mg/m^2 I.V on Day 1 and Cyclophospahmide infusion 1g/m^2 on Day 1.Repeat these every 3 weeks for a year [1,11,13].

5. OSTEOGENIC SARCOMA

This is the commonest primary malignant bone tumour in children [10] and in Nigeria [14,15]. It is commonly seen during the adolescent growth spurt with almost equal sex distribution. It usually involves the metaphysis of long bones e.g femur (50%), tibia (30%) and humerus (10%) [10]. Predisposing factors include hereditary retinoblastoma, Paget's disease, multiple hereditary exostosis, multiple osteochondromatosis (Oilier disease), osteogenesis imperfecta, prior radiation for Ewing Sarcoma or Brain tumour, Li-fraumeni syndrome, Fibrous dysplasia and Rothmund-Thomson Syndrome [4,16].

Clinical Features

1. Bone swelling that is -localized, painful and warm to touch.
2. Limitation of movement
3. Limping gait
4. Joint effusion
5. Pathological fractures
6. Features of pleural effusion, pneumothorax due to early metastases to the lungs.

Investigations

1. Plain x-ray to show:
- mixed osteoblastic and osteolytic changes at the metaphyseal region of long bones. In 20% of cases it is either purely blastic or lytic changes [10]
- classical sunburst appearance with periosteum elevation i.e Codman's triangle
- evidence of soft tissue involvement in ¾ of patients [10].
2. Chest x-ray to rule out pulmonary involvement
3. CT scan of the bone to delineate the magnitude of medullary and soft tissue involvement
4. Radionuclide scan which may detect bony metastases or the rare Polyostotic form
5. MRI
6. Bone biopsy (preferably an open biopsy) is confirmatory
7. Complete blood count
8. Serum Chemistry is usually normal though ALP or LDH levels are usually elevated. ALP level may be used as a marker of the response to therapy [16,17]
9. Erythrocyte sedimentation rate (ESR) is normal. [17]

Treatment

Radical surgery with aggressive chemotherapy using a combination of Methotrexate, Cisplatinum, Doxorubicin, Bleomycin, Cyclophosphamide, Actinomycin-D and Folinic acid in one complete cycle of 84 days in up to 4 cycles [4].

Note however that Osteosarcomas are poorly radiosensitive.

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