Childhood Malignancies In Nigeria

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INTRODUCTION

Childhood malignancies pose an important public health problem worldwide, accounting for significant morbidity and mortality in both developed and developing countries. In a recent European study spanning over a period of two decades and involving 33 population based cancer registries in 15 European countries, a significant increase in the incidence of childhood cancer was identified [1]. The burden of childhood cancer in developing countries such as Nigeria is often not fully appreciated because of the overwhelming preponderance of communicable diseases, which still account for the majority of deaths among children less than 15 years of age[2]. Indeed, the problem of childhood cancer in Nigeria has received relatively little attention from clinicians in the past, which raises an important need for enlightenment of all medical professionals concerned with the management of paediatric cancer patients[3]. This demand is all the more important because increasingly effective control of communicable diseases may result in an increasing frequency of childhood cancer in our environment, similar to what is being observed in developed countries [4,5,6].

It is estimated that there are 100,000 new cases of cancer per year in Nigeria, which will increase to about 500,000 cases annually by the year 2010 [7]. A critical review of published data from Nigerian cancer registries and several other publications have confirmed some changing trends in the relative incidence of major cancers in both adults and children [7]. In the first detailed analysis of childhood malignancies from Nigeria, by Sinnette in 1967 it was observed that cancer accounted for 2.5% of paediatric admissions and 3.9% of childhood fatalities in the University College Hospital, Ibadan [8]. These rates were triple the respective rates in some American paediatric centres.

It is difficult to obtain reliable data on childhood cancer from developing countries for several reasons. Firstly, in developing countries, accurate population figures are largely unavailable and therefore, incidence rates of childhood cancer thus cannot be computed [2]. Secondly, the definition of what age range represents childhood varies widely from one study to another. Most international studies accept less than 15 years (i.e. 0-14 years) to represent childhood and 15-19 years to represent adolescence.

It must be appreciated that childhood cancer comprises not one disease entity, but rather is a spectrum of different malignancies. Childhood cancers vary by type of histology, site of disease origin, race, sex, and age [9].

Table 1 displays the classification of childhood cancer according to the guidelines of the International Agency for Research on Cancer [10]. The broad classes of childhood cancer include haematopoietic-lymphoid neoplasms, central nervous system (CNS) neoplasms, sympathetic system neoplasms, retinoblastoma, renal neoplasms, hepatic neoplasms, malignant bone tumours, soft tissue sarcomas, germ cell/trophoblastic/gonadal neoplasms, carcinomas and other unspecified neoplasms.

LEUKAEMIA

Childhood leukaemias constitute about 4% of childhood tumours among Nigerian children [11]. The ratio of acute-to-chronic leukaemia is 20:1 during childhood, and acute lymphoblastic leukaemia (ALL) is the single most common subtype of leukaemia, accounting for 87% of acute leukaemias [12]. Although there has been an increase in the incidence of leukaemias with a decline in the leukaemia-lymphoma ratio from 1:11 to 1:6, the relative frequency of leukaemias in Nigerians is significantly much less than among European and North American children, among whom leukaemia is by far the most frequent childhood malignancy [13,14]. One in 2000 Caucasian children will develop leukaemia before age 15 years [15]. Predisposing factors to childhood leukaemia include Trisomy 21, high birth weight, male sex, and maternal irradiation during pregnancy. The genesis of acute leukaemia involves a two-hit model comprising inherited mutations of the ***TEL*** and ***AML1*** genes in about 25% of cases and subsequent early

postnatal childhood infection [15].

Acute lymphoblastic leukaemia (ALL) is a neoplastic clonal proliferation of immature precursor B, T or "null" cells incapable of further maturation in the bone marrow. Accumulation of these immature lymphoid cells results in depletion of normal haematopoietic elements [(16)]. About 70% of all cases of ALL are of B cell lineage, while 10-25% of cases are of T cell lineage [17]. ALL is rare before the age of 4 years in blacks. The typical clinical presentation is with fever, bleeding, splenomegaly or hepatosplenomegaly. Infection and bleeding are the consequences of pancytocytopenia [16,17]. Leukaemic infiltration may also affect the craniospinal axis, causing facioparesis, cord compression, meningeal infiltration or intracranial space occupying lesions [17]. A good outcome is associated with hyperdiploidy (chromosome number greater than 50), Trisomy 4 and 10 and translocation involving chromosomes 12 and 21 t(12;21)(p13;q32). An adverse outcome is linked to extreme hyperdiploidy (near triploidy or tetraploidy), the Philadelphia chromosome, and translocation involving chromosomes 4 and 11 t(4;11)(q21;q23) [16]. Additional adverse features among Nigerian children is the frequent occurrence of hyperleukocytosis, age less than 2 or greater than 7 years, L2 morphology and low periodic acid-Schiff reactivity of the lymphoblasts [13].

Chronic myeloid leukaemia is relatively rare in childhood, accounting for less than 5% of all childhood leukaemias [12,17].

LYMPHOMA

Lymphomas, of which the majority are Burkitt's lymphomas, accounted for 45% of all childhood cancers in Ibadan between 1973 and 1990 [(12)]. Burkitt's lymphoma is the most common childhood neoplasm in several studies [3,5,6,18]. Indeed, Burkitt's lymphoma may still be regarded as being endemic in most parts of Tropical Africa [19,20]. The incidence of Burkitt's lymphoma has declined from 51% of childhood tumours to 19.4%, although Burkitt's lymphoma remains the single most common childhood neoplasm. This decline is presumably because of improved socio-economic conditions and control of malaria in children [11,17].

Over 90% of childhood lymphomas are non-Hodgkin's lymphomas and only 8% are cases of Hodgkin's lymphoma. Lymphomas show a male predominance with male-to-female ratios of 1.7:1 for Burkitt's lymphoma and 5:1 for Hodgkin's lymphoma. Whereas Hodgkin's lymphoma and other non-Burkitt's lymphomas have a modal frequency between 9-14 years of age, Burkitt's lymphoma has a modal frequency at the age of 8 years [12]. Whereas lymphomas are the most common cancers in African children, they are only the third most common cancers in Caucasians[9].

Burkitt's lymphoma is a neoplasm characterised by clonal expansion of mature peripheral B lymphoid cells of post germinal centre origin. Reputedly, Burkitt's lymphoma is one of the most rapidly proliferating neoplasms known to man, with a tumour cell doubling time of just 24 hours.

Burkitt's lymphoma is believed to result from the interplay of three factors; namely, Epstein–Barr virus (EBV) infection, malarial infection and a chromosomal translocation involving the *c-myc* oncogene on chromosome 8 and any one of three genes, viz., the heavy (***H***), kappa or lambda light chain genes on chromosomes 14, 2 and 22, respectively [11]. This translocation results in up regulation of the activity of the *c-myc* oncogene.

Clinically, Burkitt's lymphoma manifests with involvement of the jaw, abdominal visceral organs, intra-abdominal and thoracic lymph nodes, ovaries, testes and terminally the central nervous system. Cytological analysis of tumour or ascitic fluid aspirates is helpful in the diagnosis of Burkitt's lymphoma [21,22]. Examination reveals neoplastic lymphoid cells having a similar phenotype to the L3 subtype of ALL (medium sized lymphoid cells displaying moderate amount of lipid vacuolated cytoplasm, with 1 to 3 prominent nucleoli). However, unlike lymphobasts, Burkitt's cells express CD19 and CD20, which are markers of mature B cells. Histological examination of tissue biopsies reveals a classical starry sky appearance [23].

CENTRAL NERVOUS SYSTEM NEOPLASMS

There was an approximately six-fold increase in the incidence of central nervous system (CNS) neoplasms in Ibadan from 2.2% to 12.9% between 1960 and 1999 [11]. Doubtless, a similar trend will also be observed in the near future in several other Nigerian centres, including the Obafemi Awolowo University Teaching Hospital Complex, Ile-Ife, with the burgeoning numbers of locally trained experts in neurosurgery, neurology, neuroradiology, neuropathology and neuropaediatrics. Astrocytomas are the most common paediatric intracranial neoplasms and account for about 39% of cases [12]. The majority of cases are hemispheric, while cerebellar, optic and pontine cases have been recorded. The location of the tumour determines the clinical presentation. For example, visual impairment (optic nerve), stunted growth and hypoglycaemia (hypothalamus), nystagmus and ataxia (cerebellum), spasticity and cranial nerve impairment (brainstem) may

occur in addition to features of raised intracranial pressure [24].

Other common neoplasms include craniopharyngiomas and medulloblastomas [12,25]. In the series of Izuora *et al.* reported in 1989 from Enugu, Nigeria, the three most common childhood intracranial neoplasms were craniopharyngioma (38%), astrocytoma (14%) and medulloblastoma (14%) [26].

About three decades ago, Akin Olufemi Williams, one of the most prolific African pathologists, and co-workers opined that the incidence of gliomas is relatively low in black as compared to Caucasian children [4,27]. This statement will need to be constantly re-evaluated by workers in the field of paediatric neuro-oncology as medical services continue to expand in scope and availability. It is very likely that the true magnitude of the problem of intracranial and other CNS neoplasms in Nigerian children is being underestimated by most studies due to the relative lack of neurological services in potential peripheral referring hospitals [12].

SYMPATHETIC SYSTEM NEOPLASMS

Neuroblastomas are malignant embryonal tumours, essentially restricted to infancy and childhood, derived from primordial neural crest cells and predominantly arising within the adrenal medulla [9]. There has been a dramatic decline in their incidence in Ibadan, from 2.6% to 0·9% between the periods 1960-1972 and 1990-1999 [4,11].

Little is known about the aetiopathogenesis of neuroblastoma. However, medication and hormones used during pregnancy have been implicated [9].

The typical clinical presentation of affected children is with abdominal mass and weight loss. Unlike nephroblastoma, which is often confined to one side, neuroblastoma often crosses the midline. These neoplasms may elaborate catecholamines, enabling their detection by assay of vanillyl mandelic acid in a 24-hour urinary specimen.

Histology reveals a malignant embryonal ("small round blue cell") tumour displaying neural differentiation as evidenced by the presence of Homer Wright rosettes and the expression of markers such as neuron specific enolase, chromogranin and synaptophysin.

Prognostic factors include age (favourable in infancy because of chemosensitivity and the occasional occurrence of spontaneous regression, but poor in older children), hyperdiploidy (good), stage of disease and *n-myc* oncogene over-expression (bad)[9].

RETINOBLASTOMA

Retinoblastomas are malignant embryonal childhood neoplasms displaying photoreceptor differentiation at light microscopic, electron microscopic, immunohistochemical and molecular levels [14,28,29]. In 1971, Dr. Alfred George Knudson, a paediatric ophthalmologist working at MD Anderson Hospital, Houston, presented a statistical analysis of 48 cases of retinoblastoma seen over a preceding 25-year interval, which led him to postulate that two mutational events were required before retinoblastoma could develop, the so-called two hit hypothesis. In the case of hereditary retinoblastomas, the first hit is an inherited or germinal mutation, which is followed by an acquired somatic mutation. In the case of sporadic retinoblastomas, both mutational events are somatic. He further went on to opine that the genes involved were what he christened anti-oncogenes, and which are currently termed tumour suppressor genes [30].

Retinoblastomas account for about 10% of all neoplasms among Nigerian children [14]. Three-quarters of retinoblastomas occur in the first five years of life, the modal age being 5 years. There is a sharp decline in frequency of occurrence of retinoblastoma with increasing age. There has been a relative increase in the frequency of retinoblastomas in Ibadan. Retinoblastomas are recognised to be both more common in black than in Caucasian children and associated with twice the mortality in blacks as in whites [28]. Although there has been an improvement in the prognosis of retinoblastoma in Ibadan with the advent of radiotherapy, the outlook for children with retinoblastoma is still bleak in comparison with what obtains in developed countries [28]. The relative increase in the frequency of this neoplasm over the past 3 decades may reflect improved diagnosis, paralleling an increased number of qualified ophthalmologists [14].

Bad prognostic factors include large tumour size, poor histological differentiation (paucity or absence of Flexner-Wintersteiner rosettes), optic nerve invasion, scleral invasion and distant metastases [31].

RENAL NEOPLASMS

About 6% of malignant childhood neoplasms in Ibadan are malignant renal neoplasms, of which over 95% are nephroblastomas [11,12]. Nephroblastomas are malignant embryonal neoplasms arising in the renal cortex from embryonic nephrogenic mesenchymal rests [32]. Histologically they are characterised by trilineage

differentiation into blast cells (small round blue cells), epithelial cells (in the form of primitive abortive renal tubules and glomeruli) and mesenchymal elements (including smooth or skeletal muscle, or rarely bone and fat). The association of nephroblastoma (Wilms' tumour) with certain specific rare congenital malformations and syndromes such as aniridia and hemihypertrophy has made it possible to delineate at least 3 specific gene loci, designated *WT1*, *WT2* and *WT3*, respectively [33].

The average age of patients (3.7 years) with nephroblastomas is about half that of patients with renal cell carcinomas (7 years), although renal cell carcinomas may also present in infancy and early childhood[12].

There is a 3 fold difference between the age standardised rates of above 10 cases per million children in Nigerians and black Americans as against 3 cases per million in East Asia [27]. Nephroblastoma was once considered an index tumour in childhood because of a purported uniform worldwide incidence, but is now recognised as showing wide fluctuations in geographic incidence [34].

Unfortunately, most children with nephroblastomas in this environment tend to present at a late stage with far advanced disease, when only palliative therapeutic measures can be instituted [14].

HEPATIC NEOPLASMS

In children under 15 years of age hepatocellular carcinomas and hepatoblastomas are the most common primary liver neoplasms, both occurring at all ages, with a peak incidence between 10-14 years of age. Whereas hepatocellular carcinoma shows a male predominance (male-to-female ratio 9:1) hepatoblastoma shows a female predominance (male-to-female ratio 1:3) [12].

Hepatoblastomas are malignant childhood liver neoplasms displaying epithelial differentiation (foetal or embryonal), with or without mesenchymal differentiation [35]. They are largely confined to the first 5 years of life, and rarely occur above the age of 14 years. Several clinical syndromes, including the Beckwith-Wiedemann syndrome, Aicardi syndrome, Budd-Chiari syndrome and Prader-Willi syndrome and synchronous nephroblastoma have been reported in association with hepatoblastoma [35].

Childhood primary hepatocellular carcinoma is rare and accounts for less than 1% of all abdominal malignancies in children aged 14 years of age or less [36]. The mean age at presentation is about 10 years and affected children generally present late with abdominal distension and hepatomegaly as the major clinical features. The prognosis is dismal, most cases dying within 2 weeks of presentation in hospital. Hepatitis B virus infection is an important aetiological factor; therefore, universal early vaccination against hepatitis B virus is necessary in Nigerian children in order to reduce the burden of chronic hepatitis B disease and hepatocellular carcinoma [36].

MALIGNANT BONE NEOPLASMS

The modal age of patients with bone neoplasms is 13 years, three quarters of them occurring between 10-14 years of age [12]. Common childhood bone neoplasms include osteogenic sarcomas (71%) and chondrosarcomas (17%). Ewing sarcoma, well recognised to be associated with a specific cytogenetic defect t(11;22), is generally uncommon in Black children [12]. By contrast, up to 30% of paediatric bone neoplasms in Caucasian children are associated with Ewing sarcoma [37].

SOFT TISSUE SARCOMAS

Malignant connective tissue neoplasms account for about 11.7% of childhood tumours and occur at all ages throughout childhood, with bimodal peaks in the first five years of life and in later childhood [11]. There appears to have been a significant increase in the frequency of soft tissue sarcomas in Ibadan over the past three to four decades, probably because of increased case ascertainment [11].

Rhabdomyosarcomas are the most common histological type of malignant connective tissue neoplasm, accounting for over 60% of cases [12,38,39]. In one series from Ibadan, the sex incidence is equal and the modal age of occurrence was 3 years [12]. In another study from Port Harcourt, there was a male preponderance with a male to female ratio of 3.2:1 [39].

Most rhabdomyosarcomas occur in the head and neck, arising in the jaw, orbit and oral cavity. Other reported sites of occurrence are genitourinary, trunk and limbs [12]. The two most common histological types are embryonal rhabdomyosarcoma (71.5%), and alveolar rhabdomyosarcoma (19%), in contrast to adults, who have a preponderance of pleomorphic rhabdomyosarcoma[39].

Less common histological types of childhood sarcomas include malignant fibrous histiocytomas, fibrosarcomas, angiosarcomas and liposarcomas [12,40].

GERM CELL, TROPHOBLASTIC AND GONADAL NEOPLASMS

Malignant germ cell or gonadal neoplasms show a female

predominance with a male-to-female ratio of 1:1.6. Intriguingly, most males with these neoplasms are less than 5 years of age, whereas females are generally above 10 years of age [12].

Germ cell neoplasms encountered in this environment include endodermal sinus tumours, testicular embryonal carcinomas of the testis, dysgerminoma and malignant sacrococcygeal teratoma. The mean age of patients with sacral neoplasms (1.58 years) is significantly lower than that of patients with other endodermal sinus tumours (5.58 years) [12]. Investigative studies from Nigeria and South Africa indicate that the incidence of malignant teratomas in blacks is relatively less than that in Caucasians [41,42]. The prognosis of malignant germ cell tumours in the Nigerian child is guarded, because of late presentation with advanced clinical stage and widespread unavailability of effective chemotherapy and or radiation facilities, even in tertiary health care centres [43].

EPITHELIAL NEOPLASMS

Malignant epithelial neoplasms are extremely rare in childhood. The nasopharynx (27%) and thyroid gland (14%) are the most common primary sites for childhood carcinomas. Other less common primary sites of origin included the salivary glands, skin and conjunctiva in descending order of frequency [12]. Cases of skin cancer occurring in childhood may occur in association with albinism and burn scars [44].

CONCLUSION

The World Health Organization (WHO) has identified aging, infections, cancer and mental health as the four major health problems confronting mankind in the 21st century [7]. Neoplastic diseases are recognised to be an important cause of mortality in sub Saharan Africa, surpassing deaths from the acquired immune deficiency syndrome, tuberculosis and malaria combined. Obviously, there are serious challenges confronting the paediatric oncologist in resource-poor settings such as Nigeria [7]. For example, at least half of children may present with advanced disease, investigative laboratory facilities and curative chemotherapy regimens may not be affordable to care givers, even if available, and the rate of default is very high [5,28,51,52]. These issues have to be adequately addressed by any meaningful national health care policy in order to improve the long-term outlook of cancer patients in our country.

TABLE 1- INTERNATIONAL CLASSIFICATION OF CHILDHOOD CANCER

I- LEUKAEMIA	Acute Lymphoid leukaemia, Acute Myeloid leukaemia, Chronic myeloid leukaemia, Other specified leukaemias, Unspecified leukaemias
II- LYMPHOMAS AND RETICULOENDOTHELIAL NEOPLASMS	Hodgkin's lymphoma, Non-Hodgkin's lymphoma, Burkitt's lymphoma, Miscellaneous lymphoreticular neoplasms, Unspecified lymphomas
III- CNS AND MISCELLANEOUS INTRACRANIAL AND INTRASPINAL NEOPLASMS	Ependymoma, Astrocytoma, Primitive neuroectodermal tumours, Miscellaneous intracranial and intraspinal tumours, Unspecified intracranial and intraspinal tumours
IV- SYMPATHETIC SYSTEM NEOPLASMS	Neuroblastoma and ganglioneuroblastoma, Other sympathetic system neoplasms
V- RETINOBLASTOMA	
VI- RENAL NEOPLASMS	Nephroblastoma, rhabdoid tumour and clear cell sarcoma, Renal carcinoma, Unspecified malignant renal neoplasms
VII- HEPATIC NEOPLASMS	Hepatoblastoma, Hepatic carcinoma, Unspecified malignant hepatic neoplasms
VIII- MALIGNANT BONE NEOPLASMS	Osteosarcoma, Chondrosarcoma, Ewing's sarcoma, Other specified malignant bone tumours, Unspecified malignant bone tumours
IX- SOFT TISSUE SARCOMAS	Rhabdomyosarcoma and embryonal sarcoma, Fibrosarcoma, neurofibrosarcoma and other fibromatous neoplasms, Kaposi's sarcoma, Other specified soft tissue sarcomas, Unspecified soft tissue sarcomas
X- GERM CELL, TROPHOBLASTIC AND OTHER GONADAL NEOPLASMS	Intracranial and intraspinal germ cell tumours, Other and unspecified non-gonadal germ cell tumours, Gonadal germ cell tumours, Gonadal carcinomas, Other and unspecified malignant gonadal tumours
XI- CARCINOMAS AND OTHER MALIGNANT EPITHELIAL NEOPLASMS	Adrenocortical carcinoma, Thyroid carcinoma, Nasopharyngeal carcinoma, Malignant melanoma, Skin carcinoma, Other and unspecified carcinomas
XII- OTHER AND UNSPECIFIED MALIGNANT NEOPLASMS	Other specified malignant neoplasms, Other unspecified malignant neoplasms

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