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Research Article

Bilateral Retinoblastoma in South Nigeria: The Facts of the Matter

Adedayo Adio[1]* and Gracia Eke[2]

[1]Department of Ophthalmology, University of Port Harcourt Teaching Hospital, Rivers State, Nigeria

[2]Department of Paediatrics, University of Port Harcourt Teaching Hospital, Rivers State, Nigeria

***Corresponding Author:** Adedayo Adio, Department of Ophthalmology, University of Port Harcourt Teaching Hospital, Rivers State, Nigeria.

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Abstract

Background: Retinoblastoma is the most common primary intraocular malignancy in children and remains the most curable of all childhood cancers. Affectation of one eye is more common than involvement of both eyes. However as uncommon as it is, both eyes must be thoroughly examined in order not to overlook anything and sometimes we find tumor in the seemingly unaffected one.

Objectives: To review the pattern of presentation of children with bilateral retinoblastoma at the University of Port Harcourt Teaching Hospital (UPTH), Nigeria, and present their treatment outcomes and the factors influencing it.

Methods: All patients with bilateral retinoblastoma admitted into the Paediatric Oncology unit of the UPTH from January 2011 to June 2019 were reviewed. Their demographics, clinical profile and outcome of treatment were analyzed using SPSS version 20.0.

Results: Six of 19 children had bilateral retinoblastoma which represented 31.5% of cases of retinoblastoma. All were mostly between 1 - 5 years (83.3%, n = 5) of Igbo ethnic extraction (n = 3,50%).

Parents were mostly middle class (66.7%) with no family history of any malignancy. A white spot in the eye (83.3%, n = 5) was the commonest presenting complaint. Half (50%) presented within 4 month of onset of the disease.

All except one had investigations carried out (83.3%) mostly ocular scans and brain CT.

All were however already manifesting bilaterally at first presentation though one presented with a fungating mass. One patient presented with loss of vision in both eyes. Most already had metastasis at diagnosis (66.7%) ranging from scleral extension (orbital spread) (33.3%) to optic nerve (33.3%). On admission, half commenced treatment immediately while others only started after a period ranging from 1 - 8 days. All received chemotherapy with only two of the patients able to get surgery (enucleation of the worse eye in our center) and radiotherapy (in another center).

Complications of treatment was mainly vomiting (33.7%) development of alopecia and rashes following the use of the chemotherapeutic agents. Few of them (n = 4,66.7%) absconded or were lost to follow up. One died at home. None completed treatment.

Conclusion: Bilateral Retinoblastoma affected only under-five children. Majority presented with whitish spot in the eyes. Despite early presentation in 83.3% of cases, there was still high mortality in this group probably due to heavier burden of therapy costs, high default rate and lack of radiotherapy facilities in the State.

Keywords: *Bilateral Retinoblastoma; Mortality; Second Eye; Port Harcourt; Nigeria*

Introduction

The burden of childhood cancers as a growing public health challenge is increasingly being recognized worldwide, including in the developing nations [1]. Retinoblastoma (RB), an embryonic tumor that develops from the immature cells of the retina, is the most common primary malignant intraocular tumor of childhood. It occurs approximately in 1:20,000 live births, has hereditary and non-hereditary (sporadic) pattern of transmission, and has no gender or race predilection. The disease is found almost exclusively in childhood as presentation is unusual after 5 years of age [2,3]. The non-hereditary form is usually unilateral (60%) while the hereditary one (40%) manifest either as unilateral or bilateral disease and is characterized by early onset [4-8]. Bilateral disease in Retinoblastoma is considered to be associated with loss of function of both alleles of the RB tumor suppression gene located on chromosome 13, although recent findings propose that epicentric factors and aneuploidy play central roles in the cause of this disease [9]. Generally, it is assumed that bilateral disease must be the heritable form. Individuals with heritable retinoblastoma carry a germline mutation in the RB1 tumor suppressor gene, and are predisposed to developing not just retinal tumors, but also pineal tumors (trilateral) and second cancers later in life. The majority of heritable retinoblastoma patients will develop retinal tumors, either benign (retinoma) or malignant (retinoblastoma) both caused by loss of the second RB1 allele in a susceptible retinal cell [10] (Figure 1).

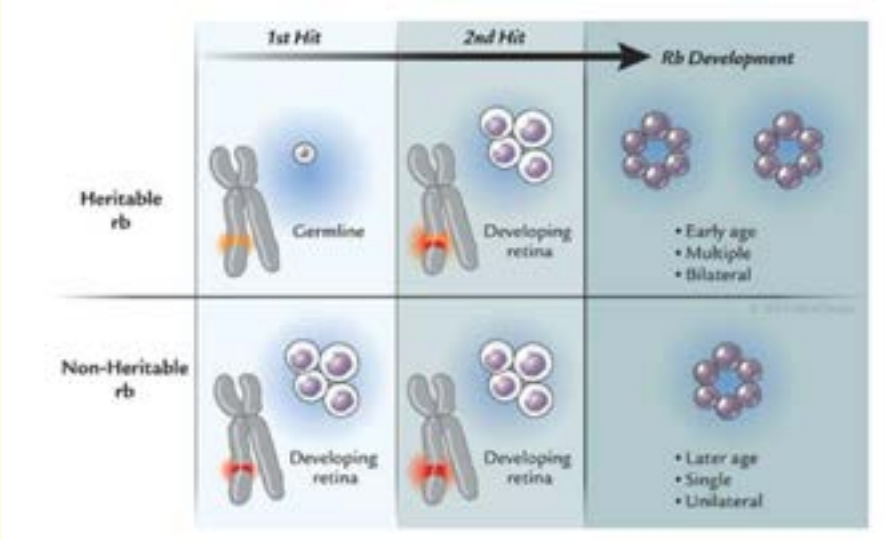

Figure 1: *Diagram showing Knudsen's 2 hit hypothesis culled from The story of retinoblastoma. The XX Edward Jackson Memorial Lecture. Dunphy EB. Am J Ophthalmol. 1964 Oct; 58:539-52.*

When the disease is found in a child less than one year of age, it is most likely going to be a bilateral disease. Therefore, each child in this age group should be carefully examined under anesthesia after dilation of the pupils [7,11].

In developed countries, RB is regarded as a rare tumour accounting for approximately 3% of all childhood malignancies and its current modern management has resulted in an improved survival to a rate of astounding 99% with more than 90-95% retaining normal visual acuity in at least one eye [8,12]. Whereas in developing nations, including African countries, where the majority of retinoblastoma cases live, it is considered one of the most frequent paediatric solid tumours with a higher incidence and survival rate estimated at just 40% [2,12,13]. This has been attributed to several factors, including lack of awareness, late presentation, parental cultural practices and tradi-

tional belief system, treatment abandonment/refusal of enucleation, absence of adequate healthcare facilities among others [5,11,12,14-16]. Sometimes also, early signs of the disease, usually a 'white' reflex or leukocoria and strabismus, are subtle and are often missed or ignored, which could lead to delay in diagnosis leading to loss of vision or even loss of life [5].

Targeted screening is also not routinely carried out by health care personnel.

Blindness on the other hand, has implications for all aspects of the child's development and is a significant burden to society in that the cost of lost productivity and of rehabilitation and education of the blind is very high and increasing. The control of blindness in children is a priority within the WHO's Vision 2020 programme, whose aim is controlling the leading causes of blindness with a view to eliminating them [17,18].

In Nigeria, despite several reports, the prevalence of bilateral RB cannot be fully ascertained as available studies are usually hospital-based and regional, showing marked variation across different regions and fraught with high rates of loss to follow-up which makes reasonable conclusions difficult. It was found to be the two most common childhood malignancies in Kano, Zaria and Shagamu, where RB accounted for 14 to 37% of cancers seen in children [19-22] while it accounted for a lesser proportion, 5 - 8% of childhood malignancies in Anambra, Jos, Ilorin and Port Harcourt [16,23-25]. Outcome of treatment on the other hand was found to be very poor, as many patients were lost to follow up after first or second course of chemotherapy [24,26] while few patients, none in some series, completed their treatment [26,27]. In addition, treatment for bilateral often times require radiotherapy (especially intensity modulated radiotherapy IMRT) not available locally at this center at this time [18]. Outcomes in terms of eyeball survival can be up to 82% especially when combined with systemic chemotherapy [28].

Patients are at risk for potentially losing vision in both eyes in addition to losing both eyes and they are at increased risk for second primary malignancies and having children with the disease. These factors have influenced how the management of bilateral retinoblastoma has evolved over decades and continues to change at present [29].

Aim of the Study

This study thus aimed to illustrate the clinical profile of bilateral retinoblastoma at a tertiary centre in southern Nigeria with the purpose of increasing awareness of the possibility of bilaterality of retinoblastoma (RB) among parents, medical practitioners and relevant authorities.

Methodology

This study was conducted at the University of Port Harcourt Teaching Hospital (UPTH), located in Rivers State, South-south region of Nigeria. It is a tertiary care hospital which serves as a major referral center for patients from within the State, with its under-15 population of 2,437,138 (47% of its population) and neighbouring states [30].

In this retrospective study, all cases of bilateral retinoblastoma reviewed at the pediatric ophthalmology clinic and thereafter admitted into the Oncology unit of the Paediatric Department from January 2011 to October 2019 were reviewed. Cases were identified from clinic records and data on each patient retrieved from hospital notes. Variables studied included biodata, duration of illness, clinical presentation, treatment offered and outcome.

Diagnosis of retinoblastoma was based on the clinical and radiologic evaluation, including ocular ultrasonography, with or without CT/MRI of orbit and brain to evaluate the extent of disease and spread in line with the International Classification of Retinoblastoma (ICRB) (Table 1).

Children with very huge tumours were given neo-adjuvant chemotherapy (chemoreduction) for 3 months prior to enucleation, while others had initial enucleation, followed by high dose chemotherapy with intravenous vincristine, etoposide and carboplatin the chemo-

International Classification for Intraocular Retinoblastoma (ICRB)	
Group A	*Small intraretinal tumors away from foveola and disc*
	* All tumors are 3 mm or smaller in greatest dimension, confined to the retina **and** * All tumors are located further than 3 mm from the foveola and 1.5 mm from the optic disc
Group B	*All remaining discrete tumors confined to the retina*
	* All other tumors confined to the retina not in Group A * Tumor-associated subretinal fluid less than 3 mm from the tumor with no subretinal seeding
Group C	*Discrete Local disease with minimal subretinal or vitreous seeding*
	* Tumor(s) are discrete * Subretinal fluid, present or past, without seeding involving up to ¼ retina * Local fine vitreous seeding may be present close to discrete tumor * Local subretinal seeding less than 3 mm (2DD) from the tumor
Group D	*Diffuse disease with significant vitreous or subretinal seeding*
	* Tumor(s) may be massive or diffuse * Subretinal fluid, present or past without seeding, involving up to total retinal detachment * Diffuse or massive vitreous disease may include "greasy" seeds or avascular tumor masses * Diffuse subretinal seeding may include subretinal plaques or tumor nodules
Group E	*Presence of any one or more of these poor prognosis features*
	* Tumor touching the lens * Tumor anterior to anterior vitreous face involving ciliary body or anterior segment * Diffuse infiltrating retinoblastoma * Neovascular glaucoma * Opaque media from hemorrhage * Tumor necrosis with aseptic orbital cellulites * Phthisis bulbi

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Table 1: *International classification for intraocular retinoblastoma (ICRB).*

therapy of choice for treatment of retinoblastoma [28] given at 3-weekly interval for 6 - 9 cycles [7] (Table 2). Parents were also advised to arrange for their ward to undergo radiotherapy which was not available in UPTH as at the time of publishing this paper. Cost of investigations and treatment were all borne by the parents. Those who had enucleation had histology to confirm the diagnosis. Genetic studies were not available.

Drug	Vincristine	Etoposide	Carboplatin
*≤ 36/12	0.05 mg/kg	5 mg/kg	18.6 mg/kg
>36/12	1.5 mg/m^3	150 mg/m^2	560 mg/m^2
+≤ 36/12	0.025 mg/kg	10 - 12 mg/kg	28 mg/kg
>36/12	0.75 mg/m^2	200 mg/m^2	560 mg/kg

Table 2: *Low and high dose chemotherapy regimen for retinoblastoma (Rb).*
**: Standard dose, +: High dose, Day 1: Vincristine, etoposide, carboplatin; Day 2: Etoposide.*

Outcomes of treatment included: completed treatment and still being followed up, loss to follow-up and died. Children who were discharged against medical advice (DAMA) as well as those who absconded from hospital and those who were not seen in the 6 months prior to collection of this data were considered lost to follow-up and abandoned treatment.

Approval for the study was obtained from the medical ethics committee of the hospital. Data was entered into a Microsoft Excel Spread Sheet and analyzed using SPSS version 20.0. Chi-Square test was used to test for significance. P values < 0.05 were considered significant. Results are presented using tables and charts.

Results

A total of 178 children were admitted for childhood cancer during the period under review out of which 169 cases with complete data were analysed (Table 2).

Number of children with ocular malignancies

Twenty-four children had ocular malignancies. Twenty-two (91.7%) of them had RB, which condition (RB) representing 13.02% of all childhood cancers seen at the University of Port Harcourt teaching hospital (UPTH). There were 8 cases of bilateral retinoblastoma representing 36.4% of all cases of retinoblastoma seen (Figure 2) (Prevalence of bilateral retinoblastoma).

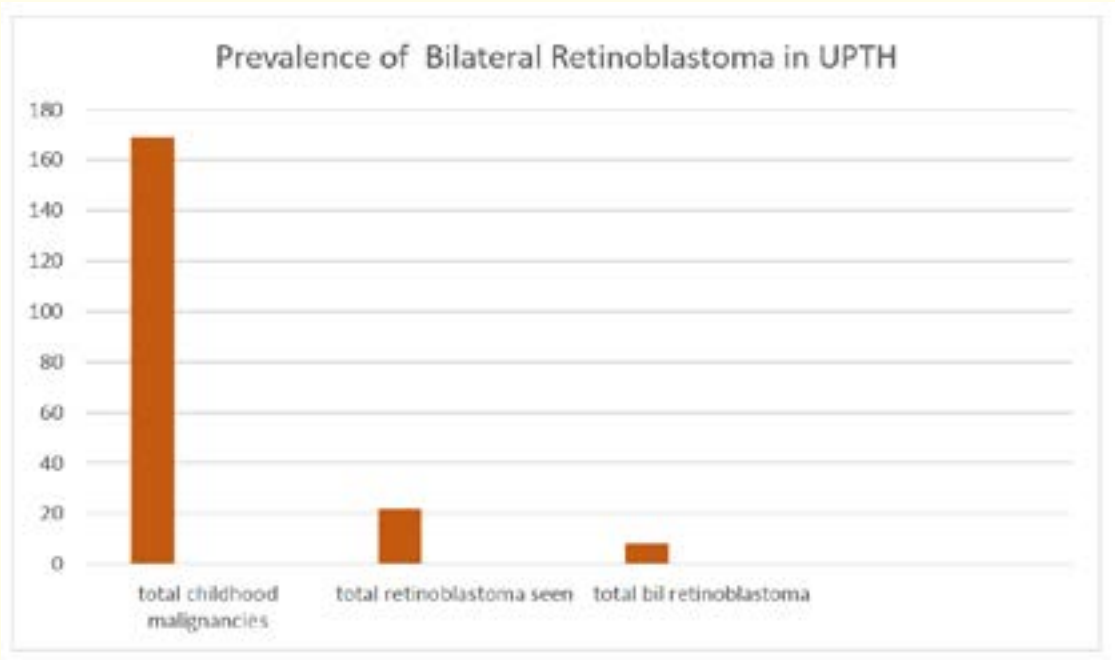

Figure 2: *Comparison of proportion of bilateral Retinoblastoma in University of Portharcourt teaching hospital (UPTH).*

Demographics of bilateral retinoblastoma (Table 3)

Age at presentation

The average age at presentation for bilateral disease was 1 year 4 months (SD 0.689) while that for unilateral disease was 2 year 7 months. The age group worst affected was the 2 year age group (7 of 8 nos, 87.5%). Only two patients were resident in PortHarcourt while others were coming from neighbouring local government areas within and outside the state of Rivers (n = 6, 75%). The gender distribution was equal.

Age at presentation	Male (%)	Female (%)	Total %
< 1 year	2 (25.0)	-	2 (25.0)
1y 1month-2 years	1 (12.5)	3 (37.5)	4 (21.1)
2y 1 month-4 years	1 (12.5)	1 (12.5)	2 (25.0)
4y 1 month-5 years	-	-	-
Total	4 (50.0)	4 (50.0)	8 (100)

Table 3: *Age and gender distribution of the study population.*

Symptoms

The commonest symptoms were white spot in the eye (leukocoria) (n = 6,75%) (Figure 3), protrusion of the eye (n = 4,50%) (Figure 4) and inability to see with one of the eyes in all 8 patients (100%). One patient presented with loss of vision in both eyes but as many as seven of 8 eventually lost vision in both eyes (87.5%) Most had been ill at home for about 6 weeks till as long as 26 months. Half (n = 4) presented in hospital before 4 month of onset of the condition (50%).

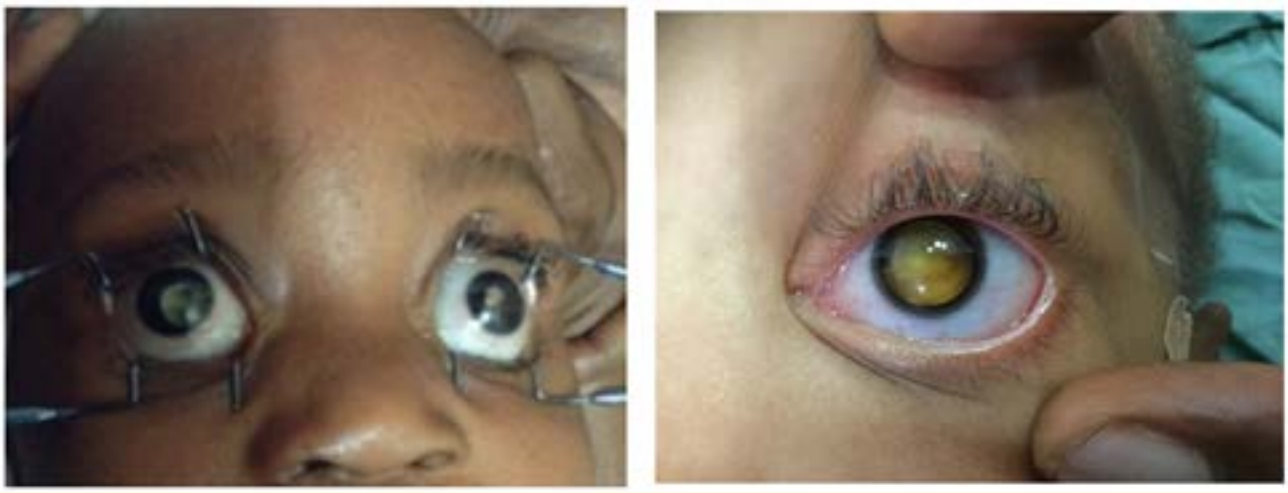

Figure 3: *Bilateral retinoblastoma ICRB classification stage D (close up view of LE).*

Family history

No family had a history of ocular and non-ocular malignancies. Both parents of 6 of these children had at least secondary school education and majority are middle class (75%). Most were either referred from a government hospital or by self to our center (n = 7,87.5%). A few had already engaged in native therapy before presentation (n = 2,25%) before presentation.

Investigations (Figure 5)

Following routine investigations, an ocular scan was more commonly affordable and ordered (n = 5, 62.5%) only 1 was able to afford brain imaging in addition (12.5%). Only three had enucleation with histology to confirm the diagnosis.

Figure 4: *Bilateral retinoblastoma with RE phthisis bulbi and LE orbital RB (ICRB classification stage E).*

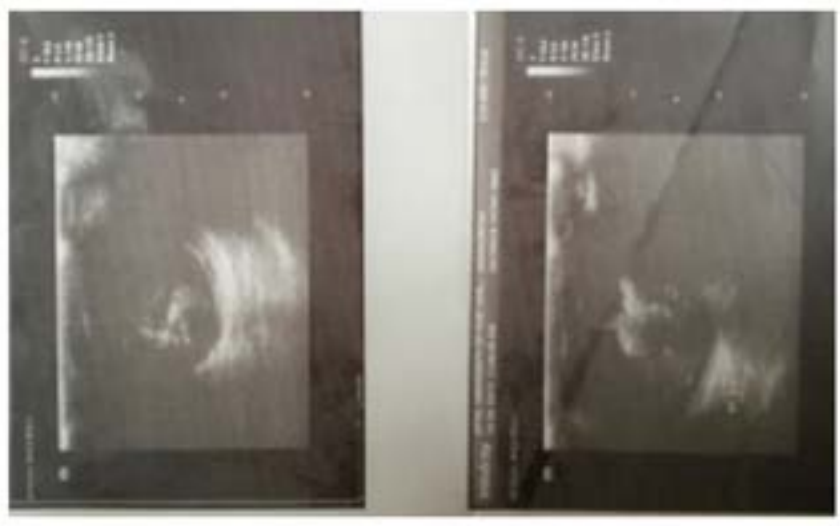

Figure 5: *Ocular ultrasound of Bilateral retinoblastoma indicating one eye more advanced with widespread intraocular calcification in BE.*

Stage (Table 4)

All disease in all 8 patients except one was group D disease in the worst affected eye while it was ranged from group B to group C in the less affected eye. There was already metastasis in 5 of 6 (n = 83.3%) involving the cut end of the optic nerve and orbit.

Patient	Right eye	Left eye	Treatment	Histopathology	Outcome
1 (Figure 4)	Stage E (phthisis)	Stage E-orbital RB	VEC-6 cycles, enucleation, no radiotherapy	Optic nerve involvement	Died
2	Stage D	Stage C	VEC 3 cycles	Orbital disease	Lost to follow-up
3	Stage D	Stage D	VEC, 5 cycles	Orbital disease	Lost to follow-up
4	Stage D	Stage E	VEC 6 cycles and palliative, intrathecal methotrexate, modified exenteration LE, no radiotherapy	Optic nerve involvement, osseous swellings on skull	Died
5	Stage D	Stage D	VEC 1 cycle	None done	Lost to follow-up
6	Stage D	Stage D	VEC 2 cycles	None done	Lost to follow-up
7	Stage D	Stage E(phthisis)	VEC 4 cycles	Optic nerve involvement	Lost to follow up
8	Stage D	Stage B	Currently on VEC regimen, enucleation planned OD and radiotherapy	On chemo reduction	On follow up

Table 4: *International Classification of Retinoblastoma (ICRB) stage of disease on presentation.*

Treatment and complications

Only 1 had radiotherapy in addition to chemotherapy (12.5%). Complications such as alopecia, anemia, vomiting and skin rash following the use of the high dose Vincristine, Etoposide and carboplatin (VEC) regimen they were given was seen in only one patient. Majority did not have any severe reaction.

Outcome

One died at home, 1 suffered a relapse 3 months after completing high dose chemotherapy for 6 months (without follow-up with radiotherapy due to financial constraints and distance) while 4 were lost to follow-up (50%). Two others were still on irregular treatment as at the time this paper was written. The one who suffered a relapse is currently on additional chemotherapy as at the time the paper was being written and has had 2 doses so far.

Discussion

Among all ocular tumors, retinoblastoma, is most common in children [31,32] anywhere in the world. In developed countries the survival rate is over 95% [32]. However, the outlook for children with bilateral retinoblastoma in developing countries is still bleak compared with developed countries, 26 years down the line after this observation was first made in Nigerian scientific literature by Ajaiyeoba., *et al*. in 1993 [33]. Its impact on the quality of life of children is undeniable. Literature is replete with the fact that childhood cancer survival rates are much lower in developing countries than in developed ones [34,35].

Series in other parts of the country, report retinoblastoma to be the most common paediatric cancer accounting for 30% of all childhood malignancies in Kano, and second most common in both Zaria (17%), and Sagamu in south-western Nigeria (21%) [20,22,36]. Whereas, highest rates in Africa were recorded in Mali (42%) and Uganda (24%) [37]. Authors partly attributed the relatively high proportions of RB in Kano and Zaria (both in northern Nigeria) to the fact that the pathology laboratories in those centres also served major eye specialist referral centres in those states.

Comparison with uniocular RB

In the present series, bilateral disease accounted for 4.7% of all childhood malignancies as against unilateral disease which accounted for 11.3% in a related study in the same center [38] which is in the same range with the 10.5% found by Owoeye., *et al*. in Ilorin [6].

Of all cases of retinoblastoma that presented, 8 of 24 cases were bilateral (33.3%) approximately a quarter of cases which makes it 1 in 3 cases will likely be bilateral. These were relatively higher than found in other sub-Saharan African countries. An Ugandan study [39] had (26% bilateral). A Senegalese study showed 20.3% [40] while a Zimbabwe study showed 16% were bilateral [41]. A Malian study showed only 10.9% was bilateral [42]. Could it be that the richer oil reserves in Nigeria is responsible for these much higher prevalence? More studies may be required to shed more light on this.

A Moroccan study however showed much higher prevalence with 5 of 12 (41.7%) presenting with bilateral disease [43]. Same with an Egyptian study (43%) [44]. It is interesting to observe that these two countries have very rich oil reserves just like Nigeria. However, a northern Nigeria (where there is relatively little crude oil found) study by Adewuyi., *et al.* [32] showed less than 5% presenting with bilateral disease. It is interesting to observe that a decade ago in our centre, no case of bilateral RB was found [26]. This new emergence of bilaterality needs to be studied so that possible causes can be preferred. Some mutation of some sort is probably being induced.

Age of presentation

Bilateral disease presented earlier in our series (1 year 4 months) when compared with uniocular (2 years and 7 months) [38]. Similar to what was found in some other studies [44,45]. Unilateral cases of RB increase significantly with increasing age at diagnosis, while bilateral cases decrease significantly in age at diagnosis [7,51,52]. However, in an Ethiopian study, the bilateral cases presented much later in life (2 years 8 months) [47].

This disparity may be associated with higher incidence of unilateral (usually sporadic) RB over bilateral cases in Africa [6]. Besides, it has been stipulated that the poor survival rate of the disease in developing nations may possibly be related to the relatively lower rate of bilateral disease in Africa as affected children do not survive to reproductive age to transmit the mutant genes to their offsprings, while poorly understood environmental factors may also be implicated [4,27]. Poverty may also account for its high prevalence in developing nations [20].

Gender distribution

The gender distribution is equal in our study as seen in south Nigerian study [34]. Same as in a Mali study [49]. This is however different from some other studies that recorded that boys more commonly had it [41-43,50]. There was a sight female preponderance in a Senegalese study [40].

Duration of symptoms

The median duration of symptoms in our series prior to presentation was 24 weeks (6months), which is rather late but of common occurrence in developing nations, and unfortunately this pattern has persisted in our environment after a decade [2,5,6,26]. This may be a reflection of the negative health seeking behaviors and cultural practices in our environment as patients often seek alternative means of healing before coming to hospital, lack of awareness of both the populace and health care personnel, among others [51,52]. The fact that initial symptoms are painless, may also explain the delay in presentation. A lower duration was reported in Kenya where a progressive reduction of the delay between onset of symptoms to presentation at the referral centre was achieved and was attributed to the awareness campaigns focusing on retinoblastoma in the country [53].

Presentation

More than half of patients with bilateral disease in this study had group D disease in at least one eye in keeping with studies by other workers [28] and metastasis at diagnosis, which is much higher than that expected in developed countries, but also higher than reports in the India (26%) and Brazil (10%) studies, which are also developing nations [2,13]. There was however relatively earlier presentation in our series.

The clinical presentation of retinoblastoma, usually with leukocoria in more than half of the patients, was also reported in these studies [2,6,14,26,34,44,45,54] it is best seen in dim lighting. Others include strabismus, deteriorating vision, changes in pupil size and, proptosis as the disease progresses, while pain is unusual [5,55,56]. Unfortunately, all patients in this study were found to have loss of vision in the affected eye, which was higher than 90% reported in DR Congo, and is likely to be related to the duration of symptoms [57]. Much lower values have also been reported, 30.8% in Western Nigeria and 2.4% in Ethiopia where, proptosis was more prevalent than leukocoria [6,57]. Proptosis is a sign of late disease. This was the most common presenting sign in Ethiopia [47], in Morocco [43] and in Zimbabwe [41].

Family history

With bilateral disease, the denial of a family history of RB we obtained is similar with other African studies [6,26]. A possible reason for this may be the usual reticence for disclosure of health issues exhibited by people in our environment. Furthermore, the lack and/or affordability of facilities for genetic studies remain a huge challenge for confirmation of this type of RB. Heritable retinoblastoma is caused by oncogenic mutations in the RB1 tumor suppressor gene [59]. In a Moroccan study, DNA was extracted from peripheral blood, and screening of RB1 mutations was performed with PCR direct sequencing of the promoter and the 27 coding exons of the RB1 gene. Ten germline mutations were discovered in a quarter of the cases tested. These mutations helped to understand the phenotypic presentations and prognosis of the cases tested. These though not common is a very important tool that should be available to patients and their families [60].

Investigations

Uptake of investigations are generally low in developing countries due to the expense which is frequently usually out of pocket. Our series showed uptake in just about half of the patients (62.5%) with only one able to pay for CT brain in addition to ocular ultrasound. A Sudanese study showed 40% uptake of ocular ultrasound and or computerized tomography of the brain/orbit [61]. Magnetic resonance imaging is best if there is extraocular disease as seen in our series and will show if there is intracranial disease or metastasis.

Treatment

Cancer treatment is generally expensive and often times requires prolonged hospital stay, especially if the child has bilateral disease. Treatment includes, depending on stage and laterality, primary chemotherapy either to facilitate enucleation or to make conservative treatment possible, intraarterial and intraocular chemotherapy, postoperative chemotherapy, enucleation and conservative treatments such as transpupillary thermotherapy, thermochemotherapy and cryotherapy, brachytherapy and external beam irradiation [28].

In the modern era [62] the rationale for neoadjuvant intravenous chemotherapy is reduction in intraocular tumor volume (chemoreduction) to allow better tumor cell killing with focal therapy (laser photocoagulation, cryotherapy, or brachytherapy). Eyes with Group A tumors are generally treated with focal therapy alone. Eyes with Group B tumors are treated with three to six cycles of VEC chemotherapy in combination with focal therapy and can result in ocular salvage rates of nearly 100%. Eyes with Group C or D tumors are treated with six cycles of VEC chemotherapy in combination with focal therapy.

The recommended treatment in bilateral disease where one eye has advanced tumors (particularly with extensive seeding) with negligible visual potential (Group D or E) is enucleation after treatment with the VEC chemotherapy for 2 - 4 cycles along with focal therapy in the better eye. The other eye which is usually better is then managed as outlined above depending on the stage. The management of patients with high-risk histopathologic features (Table 1, ICRB classification) has varied from close observation to, more commonly, chemoprophylaxis with six cycles of the low-dose CEV chemotherapy. Treatment options for extraocular retinoblastoma with overt orbital disease (like some of the patients in our series) and preauricular or cervical lymph node extension include intravenous chemotherapy which may be given for up to 9 cycles with maintenance chemotherapy dose given if recurrence is noted after regression from time to

time as determined by the treating consultant on a case by case basis in addition to external beam radiation therapy (EBRT) given in a cumulative dose of 4000 - 4500 cGy in a 200 cGy fraction per session. The prognosis of patients with metastatic retinoblastoma with CNS involvement is poor with conventional intravenous chemotherapy and radiation therapy alone; however, consolidation with high-dose chemotherapy with autologous hematopoietic stem cell rescue (AHSCR) is deemed as a promising strategy to improve survival outcomes. Lastly, extraocular retinoblastoma with CNS involvement (prechiasmatic lesion, CNS mass, and/or leptomeningeal dissemination) and trilateral retinoblastoma have a very poor prognosis despite aggressive multimodality treatment comprised of intensive induction chemotherapy followed by consolidation with high-dose chemotherapy and AHSCR. The contribution of EBRT is unclear in this group. Generally, EBRT should be avoided as much as possible especially in infants because of the higher risk of second non ocular malignancies, affectation of bone growth with the possibility of inducing hemifacial hypoplasia, and asymmetry in addition to dry eye and glaucoma.

Generally, our patients do not have access to this sort of ideal treatment and this contributes to the high mortality rate we observe.

This is because parents/caregivers have to bear the costs of treatment including drugs, diagnostic investigations, meals, transportation and hospitalization. Thus, many families of affected children in resource poor countries experience financial difficulties, as health insurance and resources to support them which is taken for granted in developed world are virtually nonexistent, and minimum wage often unrealistic, further compromising survival. However, Kaplan-Meier estimates of eye survival of Group D eyes in bilateral patients at 12 months is 82% but worsens at 60 months follow up when eye survival is estimated to be 68% [28].

However, treatment with the VEC regimen vastly improves the outcome of the disease. In a Ugandan study, this was demonstrated with the marked vision preservation shown after the use of this regimen with improved survival and vision preservation [62]. The treatment for patients with bilateral involvement must be tailored more to the preservation of useful vision in at least one eye especially when presentation is generally late; although enucleation is performed routinely on the more-affected eye, great effort is made to preserve vision in the other eye. Many of these children are irradiated for this reason though it has its own side effects. Vision, even limited vision, is very important [18]. However, facilities offering these service are very few. A study in Senegal also stated absence of radiation facilities [40]. In Nigeria as at the time of writing this paper, radiation therapy facilities are very erratic and unreliable.

Histopathology

In a clinicopathologic series that was reported elsewhere [34], Eighteen percent of patients had bilateral neoplasms. In addition, this group was significantly younger than those with uniocular disease in another study similar to our study [38]. Optic nerve involvement was found in 78% of cases who had histology. In our series, the two who had enucleation had optic nerve involvement.

Follow-up/outcomes

Bilateral retinoblastoma requires very close follow-up being a heritable disease after therapy after regression of the RB, 3 monthly follow-up should be scheduled up to 3 years, 6 monthly till 5 years and yearly for life thereafter. When this is adhered to, recurrence can easily be picked up on time and addressed. Follow up has been a very big challenge in our series and many other studies especially in developing countries. Mortality as a result of retinoblastoma has therefore been high in Africa because diagnosis is always late (most presented with advanced disease) and it is difficult to follow-up the patients. However, in some areas, follow-up is quite good with very few lost/absconding [39]. This maybe because of better systems in place with determined social service in place. Mortality was higher in those with bilateral disease as seen other studies also [39,42].

Without vision, a lot of vision related tasks are not learnt spontaneously. The outcomes are found to be a lot better when systemic treatment (shown to demonstrate a high rate of globe preservation with generally acceptable complications with many eyes retaining functional vision) is also administered. The use of vincristine etoposide and carboplatin both in standard and high dose depending on the high risk factors present has markedly improved the outcome for those who make efforts to complete their treatment [28]. Despite early

presentation, majority died in this series. This was the case also in another study [33] where two thirds died (56.8%, 25 of 44 children). A Mali study has however shown that early enucleation maybe better than delaying treatment. Delayed enucleation and refusal of adherence to treatment are still major concerns and remain a barrier to improving overall patient survival [49].

In Africa, although the survival has increased over the last few years [40] where over half were documented to have survived (31 of 59, 52.5%). Lack of access to medical facilities, lack of education about the need for early medical attention and cultural resistance to enucleation (since presentation is late) however continue to contribute to an epidemic of extra ocular disease at diagnosis in the developing world [43]. However if interventions programs are organized and community awareness increases, there will likely be earlier presentation and better outcomes as demonstrated in a South African study where fewer patients required radiotherapy (usually a high maintenance equipment) due to less advanced disease/earlier presentation [63].

Conclusion

Establishment of a National Retinoblastoma Programme or similar initiative as done in some African nations that resulted in favourable outcomes such as early detection, prompt referral, increased treatment and follow-up compliance is necessary to minimize mortality and ensure they better survive is ideal [48,53,58]. In addition, a National awareness program is important.

All children with RB present before their 5th birthday in our environment. Late presentation with loss of vision and proptosis were prevalent. A marginal improvement in outcome was noted while high default rate and lack of focal therapy for intraocular disease and radiotherapy for extraocular disease in the State has remained important challenges to completion of therapy. There is an urgent need to increase awareness of both the populace and health care providers with prompt referrals to facilitate early detection and implementation of curative therapy. Free health care for all childhood cancers with social support to ensure completion of therapy are also recommended to improve outcome in Africa. Strategies to help improve outcome for retinoblastoma in our center such as provision of relevant equipment, proper training in its use, public awareness and team approach are advocated [61,65].

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