BOHR International Journal of Current Research in Optometry and Ophthalmology
2022, Vol. 1, No. 1, pp. 62–66
https://doi.org/10.54646/bijcroo.017
www.bohrpub.com

Scenario of Retinoblastoma Among Bangladeshi Children – A Single Center Experience of 10 Years

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Abstract.

Background: Retinoblastoma is the most common intraocular tumor of childhood and most detected cases are from Indian subcontinent. Here we explore the presentation of retinoblastoma with its histopathological features and treatment outcome in a tertiary eye care center in Bangladesh.

Method: This was a retrospective study of 70 eyes of 60 patients in a ten years period from 2006 to 2016 who had met the criteria regarding demographic profile, clinical presentation, management and histopathology. Tumor was classified based on IIRC (International Intraocular Retinoblastoma Classification) for intraocular tumor and IRSS (International Retinoblastoma Staging System) for extraocular tumor by reviewing the data revealed from EUA, imaging and histopathology.

Result: The mean age of presentation was (Table 1) 31.3 ± 21.68 months, range was 4 months to 96 months and the most frequent presenting age was 12 months. Fifty three percent of children presented between 13 months and 59 months. Mild male predominance was 53.3% (n = 32). Unilateral cases were 71.3% (n = 43) and 6.7% (n = 4) of patients had positive family history. The most common presenting sign was leucocoria (85%) followed by strabismus (18.3%) and proptosis (13.3%). Fifty five (91.6%) children presented with intraocular tumor and 64.9% were with Group E. Enucleation (91.6%) was the prime treatment modality and histopathological risk factor was positive in 51.7% cases among 63.3% cases of primary enucleation. Fifty percent of treated children were in regular follow up.

Conclusion: Most children presented delayed and prime treatment modality was enucleation. Only half of the patients were in regular follow up. Generation of awareness, proper referral, information regarding treatment availability and early detection of cases can increase the survival rate and globe salvage.

Keywords: Retinoblastoma, delayed presentation, enucleation, histopathological risk factor, early detection.

INTRODUCTION

Retinoblastoma is the most common intraocular tumor of childhood and represents 11% cancers developing in the first year of life [1]. Incidence rate is 1: 16000 to 1: 18000 live birth [2, 3]. The distribution of retinoblastoma in different areas of the world is different with a higher incidence in Africa, India and native America [4]. According to World Health Organization(WHO), 66% children present before 2 years of age and 95% before 5 years of age. Among different presenting signs, leucocoria (white pupillary reflex) is the most common. In majority of cases, retinoblastoma presented as unilateral or unifocal and is usually non- hereditary. But 12% of sporadic unilateral cases may involve a germ-line mutation [5]. In bilateral or multifocal cases 25% patients present germ-line mutation in RB1 gene [6]. This tumor was uniformly fatal once, but now a days due to improved treatment methods it has become one of the highest survival cancers among all pediatrics malignancies [1, 7, 8]. In developed countries the survival rate is about 95% with a high ocular salvage [9]. But for developing countries it is still a challenge due to

Table 1. Demographic profile of patients (n = 60).

Characteristics	Number of Patients
Age	
Mean presenting age	31.33 ± 21.680 months
Presentation(months)	
0–12 months	18 (30%)
13–59 months	32 (53.3%)
60 months and above	10 (16.7%)
Mean age	31.3 months
Unilateral	34.3 months
Bilateral	16.7 months
Lowest presenting age	04 months
Highest presenting age	96 months
Most frequent presenting age	12 months (18%)
Sex	
Male	32(53.33%)
Female	28 (46.66%)
Family history	
Yes	04(6.7%)
No	56 (93.3%)
Tumour laterality	
Unilateral	43 (71.7%)
Bilateral	17(28%)
Eye involvement	77
Right	37 (48%)
Left	40 (51.9%)

Table 2. Presentation of patients (n = 60).

Presentation	Number
Leukocoria	51(85%)
Squint	11 (18.3%)
Proptosis	8 (13.3%) E
Secondary glaucoma	5 (8.3%)
Endophthalmitis	05 (8.3%)
Orbital cellulitis	03 (5%)
Hyphema	02(3.3%)
Phthisis	02 (3.3%)
S/P Enucleation	02(3.3%)

More than one sign was present in some of the patients at the time of presentation.

delayed presentation, lack of organized treatment facilities and economic factors. More than 50% of patients who presented late of them die from the disease [10]. Bangladesh is a developing country of South- East Asia and dealing with the same problems like other developing countries in managing the retinoblastoma cases. But as far as authors are concerned, there are no detailed published data regarding presentation of retinoblastoma in Bangladesh. In this article the demographic profile, clinical features, treatment modalities and histopathological outcome of retinoblastoma cases in a tertiary eye hospital of the country are evaluated.

MATERIALS AND METHOD

This was a hospital based retrospective study done by Orbit, Oculoplasty and Ocular Oncology department of Chittagong Eye Infirmary and Training Complex of Bangladesh. Data of 10 years from 2006 to 2016 were collected. In this period the hospital MRD showed 350 children were diagnosed with retinoblastoma, but completed were data found only in 60 children. The study was approved by the local institutional review board (IRB) and conducted according to the principles of the 2013 revision of the Declaration of Helsinki. These data reflects the scenario of retinoblastoma before establishment of collaborative retinoblastoma center in this institution which was established in 2017. Inadequate data were excluded from the study. Data included, demographic profile: age and sex; tumor laterality; presenting complaints; grouping and staging of retinoblastoma; treatment received and histopathological findings. Tumor was classified based on IIRC (International Intraocular Retinoblastoma Classification) for intraocular tumor and IRSS (International Retinoblastoma Staging System) for extraocular tumor by reviewing the data revealed from EUA, imaging and histopathology [11, 12] Bilateral and extraocular unilateral diseases which needed chemotherapy, were treated in collaboration with Oncology department of Chittagong Medical College hospital. Unilateral and bilateral intraocular cases were treated with local therapy like green laser, cryotherapy and surgery like enucleation or exenteration. Statistical analysis was done by SPSS.

RESULT

A total of 77 eyes of 60 patients were included in this study. Unilateral cases were 71.7% (n = 43) and bilateral were 28% (n = 17). Male babies were 53.3% (n = 32) and female were 28(46.7%); male: female ratio was 1.4: 1.

The mean age of presentation was 31.3 months and range was 4 to 96 months. Bilateral cases presented earlier (mean age 16.7months) than unilateral (mean age 34.3 months) cases.

Among 60 patients 30% (n = 18) of patients presented at or below 12 months of age, 53.3% of (n = 32) patients between 13 to 59 months of age and 16.7% (n = 10) of patients at or above 60 months. The highest presenting age was 96 months, lowest was 4 months and most frequent was 12 months (18%). Four (6.7%) patients had positive family history of retinoblastoma. Left eye (51.9%) involvement was more than the right eye (48%). The most common presentation was leucocoria (85%) followed by squint (18.3%), proptosis (13.3%), secondary glaucoma (8.3%), endophthalmitis (8.3%), orbital cellulitis (5%) and phthisis bulbi (3.3%). Two (3.3%) patients had previous history of enucleation of one eye.

Most patients (73.3%) presented to us within 6 months of onset of symptom, 20% of patients within one year and 6.6% of patients presented after one year.

Table 3. Grouping, staging and treatment received (n = 60, eyes 77).

Tumour location (n = 60)	Number
Intraocular	55 (91.6)
Extraocular	4 (6.6%)
Distant metastasis	1 (1.6%)
IIRC (e = 77)	
Group A	0%
Group B	8 (10.4%)
Group C	5 (6.4%)
Group D	9 (11.7%)
Group E	50 (64.9%)
IRRS (n = 60)	
Stage 0	0%
Stage 1	28 (46.7%)
Stage 2	27 (45%)
Stage 3	4 (6.7%)
Stage 4	1 (1.6%)
Treatment (n = 60)	
Focal therapy	22 (36.6%)
Surgery	58 (96.6%)
Enucleation	55 (91.6%)
Primary	38 (63.3%)
Secondary	17 (28.33%)
Exenteration	03 (5%)
Chemotherapy	27 (45%)
Radiotherapy	07 (11.6%)

More than one variable was present in some of the eyeballs.

Fifty five (91.6%) children had intraocular tumor, 6.6% (n = 4) had extra ocular and one 1.6% (n = 1) patient was with distant metastasis. Grouping and staging showed (Table 3), 10.4% (n = 8) eyes presented with group B tumor, 6.4% (n = 5) eyes with Group C tumor, 11.7% (n = 9) eyes with Group D tumor and 64.9% (n = 50) eyes with Group E tumor. Most patients presented at stage 1 (46.7%), followed by stage 2 (45%) and stage 3(6.7%). Only one child presented with bone metastasis. Among 60 patients, 96.6% (n = 58) of patients were treated with surgery followed by chemotherapy (45%), local therapy (36.6%) and radiotherapy (11.6%) (Table 3). Histopathological finding showed that out of 41cases of primary enucleation and exenteration, 51.7% (n = 30) of patients were histopathological risk factor (HRF) positive. Twelve patients (20%) had massive choroidal invasion, 11.7% (n = 7) had retrolaminar invasion, 15% (n = 9) had both choroidal and prelaminar involvement and 8.3% (n = 5) patients had optic nerve cut margin positive for tumor. Poorly differentiated (36%) cases were predominant (Table 4).

Table 4. Histopathological findings (eyes underwent surgery = 58).

HRF	Number
Positive	30 (51.7%)
Rosette	
Homer-write	4 (6.8%)
Flexner-winterstainer	13 (22.41%)
Both	12 (20.6%)
Poorly differentiated	21 (36%)
Undifferentiated	0
Necrosis	4(6.8%)
Completely regressed	4(6.8%)

More than one histological findings was present in some of the eyeballs.

DISCUSSION

In Bangladesh, there are no established data depicting the incidence of Retinoblastoma in the country. India is our neighboring country with a very high incidence and it is more than 1400 cases of 8000 new cases in the world every year [13]. More than 40% cases in the world are detected in the Asia- Pacific region [14]. In this paper we are sharing our 10 years' experience before establishing the RB Center in our institute. In this study the majority were unilateral cases (71.7%) than the bilateral being (28%) which is similar to some studies done in Asian countries [15, 16]. Studies from other area also showed that unilateral presentation is 70%–75% [17]. Regarding sex, one study based on retinoblastoma registry showed no sex predilection [18]. But a recent study by Global Retinoblastoma Study Group showed some male predominance in Asian countries (1.28) especially in India (1.52) [19].

Our study showed the male: female ratio was 1.4:1 which is similar to literature review.

The average age of presentation in this study was 31.3 months. One recent article from India showed that it is ∼35 months [20] though few other Indian articles showed the range is 29–33 months [21, 22]. Fifty three percent of our children presented between 13 months to 59 months which is similar to the finding of Nidhi et al.[23]. Our sixteen percent patients presented at more than 5 year of age which is 11% by Sing et al. in India and 3.5% by Bonanomi et al. in Brazil .[20,24]The delayed presentation in our study was 96 months and 16.7% (10) of patients presented after 5 years. Poverty, lack of education and lack of awareness may be the cause of delayed presentation. According World bank, Bangladesh has reached to the lower middle – income country (2015) and is on the tract to graduate from the United Nation's Least Developed Countries (LDC) in 2026. By this time poverty has declined from 44% (1991) to 15% (2016) .The data of this study represents the time period when poverty was more than present situation and it may have impacted on the education, awareness and lifestyle of the people (Table 2).

Positive family history was present in 6.7% (4) patients which is comparable to 4.09% in India, 6.6% in Singapore and 4.8% in Iran [20, 25, 26]. Leukocoria (85%) was the commonest presentation, followed by strabismus (18.3%) which is similar to studies done in both Western and Asian countries [27, 28]. Different literature showed leucocoria

ranges from 22.6% [29] to 97.9% [30] and strabismus from 5.6% [29] to 26% [31].

We also found proptosis in 13.3%, both glaucoma and endophthalmitis in 8.3% and orbital cellulitis in 5% patients as presenting sign. All those are considered as late and advanced presentation of retinoblastoma. According to Abramson et al. retinoblastoma can present as other uncommon or rare sign such as anisochoria, heterochromia iridis, inflammatory signs, nystagmus, microphthalmos/buphthalmos, proptosis, orbital cellulitis, hyphema, ptosis, aniridia, phthisis bulbi and vitreous haemorrhage etc which was studied in 1265 patients [32].

As a presenting sign, proptosis is found in very low frequency in some developed countries such as USA (0.5%) [32] and South Korea (1.4%) [33] in contrast to some other developing countries such as Nigeria (44.2%) [34], Pakistan (52.8%) [29] and Thailand (26.7%) [35]. The unusual cases are confirmed by detailed history, examination under general anesthesia, B-scan ultrasonography and CT or MRI scan. CT and MRI also helped in detection of extra ocular extension.

It is suggested that tumor involvement in anterior segment and vitreous seed cause the feature of endophthalmitis or pseudohypopyon. The necrotic changes in the ciliary body root trigger an inflammatory response to adjacent soft tissue causing the feature of orbital cellulitis [36]. The necrotic tumor can also go outside the eye by trabecular meshwork and may cause this feature. The tumor necrosis may also lead to neovascular glaucoma, hyphema and vitreous haemorrhage [37, 38].

In this study, among 77 eyes 91% of eyes presented with intraocular tumor and 64% of them were in Group E based on International Intraocular Retinoblastoma Classification which represented advanced disease [39]. Forty six percent patients were in stage I and 45% were in stage II according to IRRS.

Most of our patients were treated with enucleation 91% (55). Among them 63% (38) underwent primary enucleation who had no potential for vision and all were unilateral cases. Seventeen (28%) patients underwent secondary enucleation either due to phthisical globe or no visual potential following chemotherapy and these were the worst eyes of bilateral cases. Enucleation was the mainstay of treatment in most Southeast Asian settings for unilateral eyes falling under category D and E [39]. Three cases underwent exenteration as parents denied chemotherapy and the procedure was done to relieve the child from discomfort. Only 45% (27) of our patients received chemotherapy as chemoreduction or as adjuvant therapy. Prior to establishing collaborative center for management of retinoblastoma at our institute, we used to refer patients to medical college hospital for chemotherapy as well as radiotherapy if needed. Referring patients to another center under oncologist was a cause of non- compliance in many instances and therefore many patients either did not report to new center or discontinue chemotherapy before completion of full course. This fact led us to the establishment of 'one stop center' where all modalities of treatment for retinoblastoma could be offered and in our experience this has increased the compliance of patients dramatically. Twenty two (36.6%) patients received focal therapy such as cryotherapy and green laser as Diod laser was not available at that time. Only 11.6% (7) patients in this study received external beam radiotherapy and this may probably be due to its higher complications of second neoplasms especially in the area of radiation [40].

Histopathological findings of our study showed, among primary enucleation and exenteration cases that 51.7% were HRF (Histopathological High Risk Factor) positive. Twelve patients (20%) were with massive choroidal invasion, 11.7% (7) with retrolaminar invasion, 15% (9) with both choroidal and prelaminar involvement and 8.3% (5) with optic nerve cut margin positive for tumor. One recent study showed that Asian Indians had a fivefold greater risk of having optic nerve invasion and threefold greater risk of massive choroidal invasion compared with Americans [41].

Regarding regular follow-up, only 50% of our patients maintained the scheduled follow-up. To increase timely follow-up, counseling regarding the disease process and importance of follow-up is necessary. Probably there was a lack of it.

This study has certain drawbacks: It was a retrospective analysis and very small patient number. This study only represents the data of a single center prior establishment of multidisciplinary treatment facilities. Majority of patients were at advanced age. Most patients underwent enucleation and many were lost due to lack of multidisciplinary facilities at the same hospital.

CONCLUSION

Though retinoblastoma is a rare disease, it may be a devastating disease not only for the affected child but also for the affected families. Most of our children presented in delay and the prime treatment modality was enucleation. Only half of the patient were in regular follow up due to lack of counseling. Generation of awareness is the first to do for early detection of retinoblastoma. For developing countries we can initiate early detection of cases by including the screening process in Expanded Program on Immunization (EPI) and community based School Eye Health program. Proper referral, information regarding treatment along with early detection will save valuable life and even sight also.

ACKNOWLEDGEMENTS

The authors thanks Prof. Rabiul Husain for continuous moral support.

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