Original Article

Retinoblastoma at a tertiary level eye centre, Nepal

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Abstract

Introduction: Retinoblastoma is the most common intraocular malignant tumor in children occurring in approximately 1 in 18,000 live births. With early detection and management, lives of many children can be saved, eyes can be preserved and vision can be restored. The study was aimed at finding out the clinical features, methods of management and outcome of the disease in a tertiary eye care centre of institute of medicine in Nepal.

Methods: A prospective case series study was done between 2014 -2017 at BP Koirala Lions Centre for Ophthalmic Studies, Institute of medicine, Nepal. The diagnosis of retinoblastoma was made on the basis of history and clinical examination. Additional information was obtained from radiological procedure whenever required. International classification of retinoblastoma (Shields) was used to clinically classify the retinoblastoma lesion and the management depended on the stage of the disease.

Results: A total of 36 patients with retinoblastoma fulfilled the inclusion criteria of the study, 23 males and 13 females with sex ratio: 0.57. Median age at diagnosis was 36±13.825 months. In 19.4% of cases the disease was bilateral. Leukocoria, red eye and proptosis were common signs observed in 46.5%, 33.3 % and 16.3% of case respectively. Enucleation and exenteration were the commonest modality of treatment. Six patients died during the course of treatment and during follow up period and 8 patients were lost before one year of follow up.

Conclusions: Despite the advances in the field of retinoblastoma, the prognosis still remains poor due to delay in presentation in our centre.

Key words: management, Nepal, retinoblastoma

Introduction

Retinoblastoma is the most common treatable intraocular malignancies of infancy and childhood. It is the important cause of ocular morbidity and even mortality in developing countries like Nepal. The incidence is approximately 1 in 18000 live births in the United States[1]. There is no significant race or sex predilection. The disease is bilateral in 20-35% of cases[2]. The average age at diagnosis is 18 months, unilateral cases being diagnosed at around 24 months and bilateral cases before 12 months[2]. Approximately 89% of patients are diagnosed before 3 years of age and around 8.5% cases are older than 5 years of age at the time of diagnosis. It is rare after 7 years of age but has been reported in patients past 50 years of age[3].

It represents 3-4% of all malignancies in children and 1% of human cancers. The retinoblastoma gene is localized in the long arm of chromosome 13, 13q14 which regulates the development of normality. Its inhibition or inactivation causes retinoblastoma to develop. There are two forms of retinoblastoma, hereditary form with autosomal dominant inheritance with complete penetrance usually bilateral and non hereditary form with 2 mutations on retinal cells mostly unilateral in 94%[4].

With early diagnosis and new methods of treatment, there has been a dramatic change in the overall management of retinoblastoma in the last decade. The documented survival rate of retinoblastoma patients has reached to

above 87-99% in developed countries[5]. Retinoblastoma represents a unique challenge in a country like ours. Delayed diagnosis and inadequate treatment invariably leads to death in these children.

Methods

It was a prospective and descriptive study over a period of 2 and half years from 18th November 2014 to 18th May 2017. The study was carried out at BP Koirala Lions Centre for Ophthalmic Studies, a tertiary eye care centre in Nepal. All the patients with clinically diagnosed retinoblastoma were included in a study. All these patients underwent examination under anesthesia. Anterior segment examination was done under microscope. Fundus evaluation was done with indirect ophthalmoscope using 20D (dioptre) lens under mydriasis which was obtained using tropicamide eye drops 0.5%. USG B-scan was done invariably in all intraocular retinoblastomas to examine the characteristic calcification within the retinoblastoma lesion. CT and or MRI scan of brain and orbit were requested whenever felt necessary in atypical and in cases with extra ocular extension suspected.

The retinoblastoma lesion was classified using International classification of retinoblastoma (Shields, Table 1)[6]. The systemic examination was completed by pediatrician and pediatric oncologist.

Table 1 International Classification of Retinoblastoma (Shields)

Group A (Small tumor)	• Retinoblastoma <3 mm in size in basal dimension/thickness
Group B (Larger tumor)	• Retinoblastoma >3 mm in basal dimension/ thickness • Macular location (<3 mm to foveola) • Juxtapapillary location (<1.5 mm to disc) • Clear subretinal fluid <3 mm from margin
Group C (Focal seeds)	• C1 Subretinal seeds <3 mm from retinoblastoma • C2 Vitreous seeds <3 mm from retinoblastoma • C3 Both subretinal and vitreous seeds <3 mm from retinoblastoma
Group D (Diffuse seeds)	• D1 Subretinal seeds >3 mm from retinoblastoma • D2 Vitreous seeds >3 mm from retinoblastoma • D3 Both subretinal and vitreous seeds >3 mm from retinoblastoma
Group E (Extensive retinoblastoma)	• Occupying >50% globe or • Neovascular glaucoma • Opaque media from hemorrhage in anterior chamber, vitreous, or subretinal space • Invasion of postlaminar optic nerve, choroid (>2 mm), sclera, orbit, anterior chamber

Table 2 Chemotherapy regimen and doses for retinoblastoma

Day 1 Vincristine + Etoposide + Carboplatin

Day 2 Etoposide

Standard dose: (3 weekly, 6 cycles):	***High-dose (3 weekly, 6-12 cycles):***
Vincristine 1.5 mg/m2 (0.05 mg/ kg for children < 36 months of age and maximum dose < 2mg),	Vincristine 0.025 mg/Kg
Etoposide 150 mg/m2 (5 mg/kg for children < 36 months of age)	Etoposide 12 mg/Kg
Carboplatin 560 mg/m2 (18.6 mg/ kg for children < 36 months of age)	Carboplatin 28 mg/Kg

Management of the disease depended on the stage of disease at the time of diagnosis. The treatment options offered was surgery, chemotherapy, radiotherapy, focal therapy and or combination of any of these mentioned. The surgery performed was either enucleation or exenteration depending on the extension of mass. Histopathological specimens were analyzed. Systemic chemotherapy either in the form of chemoreduction, the process of reducing the volume of tumour; or in the form of adjuvant chemotherapy to minimize the risk of metastasis in patients with high risk histopathologic characteristics was done. There are different protocols in chemotherapy. The chemotherapeutic agents used in this study was vincristine, etoposide and carboplatin in combination for 6 cycles[7-10]. Standard dose chemoreduction was provided in international classification Group C[10]. In high dose chemoreduction, the dose of etoposide and carboplatin is increased. This is indicated in international classification Group D or higher tumors[10].

Chemoreduction regimen and doses for retinoblastoma used in the study is given in Table 2. Laser photocoagulation was done for tumours located posteriorly, 4mm in basal diameter and 2 mm in thickness[2,10]. Radiation therapy wherever indicated was referred to one of the cancer hospitals in town. Loss to follow up was defined as not having seen within the 3 months prior to data collection. Ethical approval to conduct a study was obtained from the institutional review board of Tribhuvan university teaching hospital, Nepal. Data entry and analysis was done using SPSS version 15 software (SPSS Inc, Chicago, IL).

Results

A total of 43 children with retinoblastoma were seen during 2 and half years of study period from November 2014 to May 2017 at BP Koirala Lions Centre for Ophthalmic Studies, a tertiary eye care centre at Institute of medicine. However only 36 children fulfilled the inclusion criteria and were analyzed in the study. The youngest baby seen was 11 days of age and the oldest one was 4 years with the mean age was 35 months. There were 23 males and 13 females with sex ratio male to female was 0.57. A majority of patients (52.8%) were between 3-5 years of age and five patients (13.9%) were below 1 year of age at presentation Table 3.

The disease was bilateral in 7 (19.4%) cases and unilateral in 29 (80.6%) cases. Among the unilateral disease, left eye was affected in 16 (44.4%), and right eye in 13 (36.1%) cases. The most common presenting feature was leucocoria 20 (46.5%), followed by red eye 13 (30.2%) and proptosis 7 (16.3%) (Table4). No parents or siblings were found to be affected by retinoblastoma in this series. The retinoblastoma lesion was classified according to international classification of retinoblastoma (ICRB, Shields)[6] following detail evaluation under anesthesia prior to management. Most of the diseases were in the Group D and Group E of ICRB (Table 5). Group A disease was diagnosed in 5 eyes of patients with bilateral involvement, Group B in one unilateral case and 2 eyes of patients with bilateral lesions. None of the cases were found in Group C. Group D disease was seen in 20 unilateral cases and 7 eyes of cases with bilateral retinoblastoma while Group E tumour was seen in 8 unilaterally involved eyes.

A majority of children with retinoblastoma presented at a stage when the tumor was confined to the eye (n=29, 80%) and remaining 20% of cases presented with orbital involvement. Chemoreduction with or without focal therapy is highly recommended these days prior to surgery[11-14]. This protocol can minimize the need for enucleation or radiation therapy without significant systemic side effect. Adjuvant chemotherapy was given depending on the histopathologic characteristics of enucleated eye ball. The management was surgical in 34 patients (94%) and one patient was treated palliatvely as he already had distant metastasis. Enucleation was the most frequently performed surgical procedure done in 30 (88%). Among them in 9 (30%) eyes, only enucleation without adjuvant therapy was performed. Exenteration was carried out in 4(12%) cases. All of them were given adjuvant chemotherapy and radiotherapy. Twenty six (75%) patients received systemic chemotherapy in the form of chemoreduction in 17 and adjuvant chemo in 9. Radiotherapy was given in 7 patients, who presented with advanced disease, mostly extraocular extension. Table 6. The patient survival was 61% (n=22) who were tumour free for at least one year following completion of the treatment. Six patients died during the study period and 8 patients lost to follow up within a year of treatment. Among 22 surviving patients, 16 (72.7%) had unilateral and 6 (27%) had bilateral retinoblastoma. Two out of 6 cases that died had extensive systemic metastasis at the time of initial presentation. The globe could be saved in 8 (18.6%) of 43 eyes that received treatment which were in group A and group B category. Among 8 eyes salvaged, 7 (87%) were the other eye of bilateral retinoblastoma cases and one eye (13%) had unilateral retinoblastoma.

Table 3 Age and gender distribution of children with retinoblastoma

Age (years)	Male	Female	Total	%
<1	2	3	5	13.89
1-2	7	5	12	33.33
3-5	14	5	19	52.78
>5	0	0	0	0
Total	**23**	**13**	**36**	**100**

Table 4 Modes of presentation of retinoblastoma

Mode	Number of eyes (n=43)	%
Leucocoria	20	46.5
Red eye	13	30.3
Proptosis	7	16.3
Asymptomatic	2	4.6
Strabismus	1	2.3
Total	**43**	**100**

Table 5 Classification of retinoblastoma according to ICRB

ICRB	Right Eye	Left Eye	Total	%
Group A	4	1	5	11.62
Group B	1	2	3	6.98
Group C	0	0	0	0
Group D	12	15	27	62.79
Group E	4	4	8	18.61
Total	**21**	**22**	**43**	**100**

Table 6 Treatment modalities used in different ICRB group

Treatment options	Right eye	Left eye	Total number of eyes
Enucleation	5	4	9
Chemoreduction and enucleation	5	6	11
Enucleation and adjuvant chemotherapy	2	5	7
Enucleation + adjuvant chemotherapy+ radiation	0	2	2
Laser photocoagulation	5	3	8
Chemoreduction +enucleation+radiation	1	0	1
Chemoreduction + exenteration+ radiation	3	1	4
Palliative (chemoreduction)		1	1

Discussion

A predominance of boys over girls with sex ratio of 0.57 was found in the study. This is comparable to other studies[15,16,17] who reported a male predominance in their series as well. The reported common age of presentation of retinoblastoma is 18-24 months[2]. The present study found the mean age of presentation of 35 months which is much higher as compared to the report by Chang et al in Taiwan[18]. In this study the age at diagnosis was 26.3 months. Another report by Lee et al. mentions19.65 months as age at presentation which is less than that noted in the present study[19]. Late presentation up to the mean age of 41 months has been reported in developing countries[16]. This could be the reason for lesser globe survival and patient survival in this study. Bilateral involvement was found in 19.4% of patients which is similar to the published reports 20-35%[20,21]. The most common presenting feature was leukocoria in this study, which was seen in 46.5% of cases. It remains the commonest mode of presentation reported in several studies[22,23]. Painful red eye and proptosis were detected in 30.3% and 16.3% cases respectively. Red eye and proptosis either of them is the signs of late presentation and are frequently seen in developing world. Badhu et al reported a higher incidence of proptosis (40%) at presentation from Eastern Nepal[15]. Leukocoria, red eye and proptosis were the common signs of the disease observed in this study. In 36 patients, 35 eyes (81%) were in advanced stage of disease (ICRB D and E) which is consistent with reports from other developing countries[24].

In developed countries, there is an increased trend towards globe salvaging treatments of retinoblastoma, as reported by Dondey et al.[25], Lee et al.[19] and Sheilds et al.[26]. In the present study, the globe survival rate was only 18.6% where as it was much higher in Iranian study (44.2%)[27], in Malaysian study (32%)[28] and in Pakistani study (22.5%)[29]. The survival rate of patients with retinoblastoma in this study was 61%. In a study by Chang et al, survival rate was 96.9% for intraocular retinoblastoma and that for the extraocular disease was 39.2%[18]. Delay in presentation is associated with higher risk of advanced disease and metastasis. Low globe salvageable rate and high mortality rate seen in this study is attributable to late presentation and lack of awareness regarding eye health education and health services in Nepal.

Conclusion

Most children with retinoblastoma was in an advanced stage of tumor at the time of presentation. Despite advances in the management protocol, the prognosis still remains poor. Consequently, empahasis on awareness regarding the disease in the community and among pediatricians could be the key to early detection and early management and improved survival of retinoblastoma patients.

Conflict of interest: None declared.

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