Retinoblastoma: changing trend in a tertiary eye centre

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Abstract

Purpose: Retinoblastoma though a rare disease is the most common intraocular malignancy in the paediatric population. The age of presentation, clinical picture and modes of treatment has been changing with time in developing countries. The purpose of this study is to evaluate the changing trend and know our current status on retinoblastoma.

Materials and Methods: Five years retrospective study of retinoblastoma patients at a tertiary eye centre in Kathmandu.

Results: Seventy-four eyes of 62 patients fulfilled the inclusion criteria. There was equal gender distribution. Eighty percent had unilateral retinoblastoma while twenty percent had bilateral retinoblastoma. Unilateral cases presented late (32.23 months) while bilateral cases presented earlier (19 months). 71% patients presented with leukocoria while only 11% presented with proptosis. Sixty-four eyes underwent destructive procedure (60 enucleation and 4 exenteration) and 10 eyes were managed with LASER.

Conclusion: Retinoblastoma patients are presenting earlier with leukocoria as common mode of presentation. Eye saving management of retinoblastoma are in rising trend in recent years.

Keywords: Retinoblastoma, Leukocoria, Enucleation, Nepal.

Introduction

Retinoblastoma is the most common intraocular malignancy in the paediatric population, representing 4% of all childhood malignancies.[1] The global incidence is approximately eleven patients per million children under five years of age.[2] Neither geography nor race have been shown to carry a predilection for the development of retinoblastoma and the main risk factor continues to be inheritance of the retinoblastoma genotype.[3] Furthermore, it has been estimated that retinoblastoma affects males slightly more often than females across various studies.[2,4] Despite the consistent incidence rate worldwide, there are significant differences in patient outcomes between the developing and the developed world.[5,6] In developing regions, such as the Democratic Republic of Congo, mortality from retinoblastoma has been reported to be as high as 92.5%.[6] Whereas in more developed nations such as Singapore and the USA, survival is as high as 91% and 96.5%, respectively.[5,7] This discrepancy in survival between countries is multifactorial. Elements identified by previous research include late presentation, lack of access to chemotherapeutic agents, poor medication compliance and the absence of histopathological staging and ancillary investigations.[6,8] To date, there have been few studies examining the incidence and survival of retinoblastoma in Nepal.[4,9,11] Given the rare nature of the disease the sample size in these studies is often small. The most extensive review of this patient group in Nepal only managed to recruit 43 patients.[11] With advances in access to healthcare and improvement of health literacy in Nepal, a re-examination of this patient population is necessary. Our study will aim to provide are more comprehensive picture of the status of retinoblastoma in Nepal.

Materials and Methods

A retrospective analysis was performed on all cases of retinoblastoma that presented at the Tilganga Institute of Ophthalmology, a Tertiary Eye Care Centre (TECC) in Kathmandu, Nepal, between April 2011 and April 2015. All case records with diagnosis retinoblastoma during the study period were reviewed. A detailed history of each patient, including the presenting complaint, history and duration of illness, family history, treatment history, age, sex, and place of residence was taken. All patients were subjected to an external ocular examination. Visual acuity was also recorded as and where possible. Anterior segment evaluation was performed via Slit-Lamp Biomicroscopy. A Haag- Streit Burn 900 or a Shin Nippon Hand-Held Slit Lamp was used. Fundus evaluation after full pupil dilation with tropicamide (1%) was performed with both direct and indirect ophthalmoscopy using a Heine with Volk +20D. When tumors were present, their size, quadrant, number, and location were noted. IOP was measured using Perkin's tonometry. Following the diagnosis of retinoblastoma, the available treatments included enucleation, exenteration, cryotherapy, photocoagulation, radiotherapy and chemotherapy. Treatment modality was planned according to stage of the disease, age at presentation, laterality, intraocular retinoblastoma, location and staging, high risk characteristics, orbital retinoblastoma, metastatic retinoblastoma, visual prognosis and systemic condition of the patient. Enucleation was done for all advanced unilateral cases or worst eye in bilateral cases. Fungating orbital retinoblastoma underwent exenteration followed by chemotherapy. All patients with bilateral retinoblastoma who underwent enucleation of one eye received LASER on other eye. A complete histopathological analysis was performed on all enucleated/exenterated specimens in accordance with the standardised "International Classification for Intraocular

Retinoblastoma" system (Shields, 2006). Patients with high risk characteristics on histopathology were identified. These patients were referred to an oncology unit of a nearby hospital for chemotherapy and radiotherapy.

All data utilized in this study was collected via chart review and then entered onto a standardized form. Data was subsequently entered into Microsoft Excel 2007. All statistical analysis was performed with SPSS Version 11.5. Descriptive statistics were represented as mean ± standard deviation.

Results

Table 1: Demographics

Patient Characteristics	
Characteristic	**Number (%)**
Gender	
Male	31(50)
Female	31(50)
Geographical Distribution	
Terai	31(50)
Hills	30(48.38)
Mountains	1(1.61)
Laterality	
Unilateral	50(80.65)
Bilateral	12(19.35)
Eye	
OD(Right eye)	39(52.70)
OS(Left eye)	35(47.30)
Mean age at diagnosis (months)	
Unilateral	32.23
Bilateral	19
All	29.67

Ninety case records of retinoblastoma were found in our study period. Of these cases, twenty-eight were excluded due to change in diagnosis, lost to follow up and incomplete data. Therefore, sixty-two cases equating to seventy-four eyes were included in the study. There was no gender bias for retinoblastoma present in our study (Males, 50%). The cases had near equal geographical distribution in the Terai and Hill regions. Only one case originated from the mountains. 80.65% of patients had unilateral retinoblastoma and 19.35% had bilateral retinoblastoma. The mean age at diagnosis for unilateral cases was 32.23 months and mean age for diagnosis of bilateral cases was younger at 19 months. (Table 1)

Leukocoria was the most common presentation (66%) followed by proptosis (14%). The time between symptom onset and diagnosis (lag time) was 54.32 days longer for unilateral cases of retinoblastoma, compared to bilateral disease. (Table 2)

Table 2: Lag time and symptoms

Lag time (days)	
Unilateral	178.48
Bilateral	124.16
All	167.95
Symptoms (%)	
Leukocoria	71
Proptosis	11
Strabismus	6
Red eye	8
Decreased vision	2
Others	2

The most common mode of primary management was enucleation (78.38%) followed by LASER (16.22%) and exenteration (5.40%). Chemotherapy was given as secondary management to 38 patients and two eyes had to be enucleated after LASER therapy (Table 3). High risk characteristics were present in 61.29% of enucleated or exenterated eyes. Choroidal infiltration was the most common of all high-risk characteristic. (Table 4)

Table 4: High risk characteristics on histology on enucleated or exenterated eyes

Primary Management	**Number of Eyes (%)**
Enucleation	58(78.38)
Exenteration	4(5.40)
Laser	12(16.22)
Secondary Management	Number of patients (%)
Chemotherapy	38(51.35)
Enucleation	2(2.70)

Table 3: Management of retinoblastoma patients

High risk characteristics on histopathology	**Number of eyes (%)**
Present	38(61.29)
Absent	13(21)
High risk characteristics	**Number of patients (%)**
choroidal infiltration	20(52.63)
optic nerve head invasion	12(31.57)
scleral infiltration	2(5.26)
invasion of optic nerve transection	3(7.89)
anterior chamber seeding	1(2.63)
iris infiltration	1(2.63)

Discussion

Although the global incidence of retinoblastoma is low, it remains the most common childhood malignancy.[12] In developed nations, retinoblastoma has the highest rate of survival for any paediatric malignancy. Reports have shown that over 99% of these patients survive, with more than 90% retaining vision in at least one eye.[12] Unfortunately, this is not the case for patients in the developing world, especially in Asia where survival rates have been reported to range between 35 and 86%.[5] The key to improved survival in the developing world centres around early recognition of the

disease and appropriate treatment. This can be achieved by improving the understanding of the status of retinoblastoma in countries such as Nepal.

Gender has not been thought to play a major role in the development of retinoblastoma. Most of the current literature supports that there is only minor sex bias for males, with ratios reported between 1.02:1 and 1.3:1.[2,4] Neither studies have shown this relationship to be statistically significant. Conversely, one study from Nigeria presented a predilection for females to develop the disease, but this has not been replicated elsewhere.[13] Our study did not reflect either of these findings. We saw an even split between males and females presenting with retinoblastoma. Furthermore, approximately 19% of the cases in our study were bilateral retinoblastoma. This is lower than the average cases of bilateral retinoblastoma reported in countries such as the USA (29%),[7] however is not as high as the most recent Nepali study by Saiju et al[4] that reported 40%. Differences in descriptive statistics regarding laterality are likely to be due to the small sample sizes used when studying this rare disease.

In countries such as Nepal, high lag times between symptom onset and presentation to a doctor and subsequent diagnosis and treatment lead to poor patient outcomes. Our study found that for both unilateral and bilateral forms of the disease, parents took an average of 5.5(±136 SD) months to attend a clinic after the onset of symptoms, and patients were on average almost 30 months old at formal diagnosis. There was no significant difference between lag times of unilateral versus bilateral cases (33.944 months and 24.75 months, respectively p=0.043) This compares poorly to developed countries such as the USA where much lower lag time has been reported (median 1.5 months).[14] A potential reason for this discrepancy is that developed nations such as the USA have routine neonatal screening programs to detect retinoblastoma before a newborn leaves the hospital.[15] However, large retrospective studies in these countries have not found routine screening for retinoblastoma to be definitively effective, with 80% of cases still being identified by a family member and not by a paediatrician.[15] Continued evaluation of such screening programs is required to determine their utility. When comparing lag times in developing countries such as the Congo, our results are favourable at approximately 5.5 months, compare to their median reported value of 9 months.[6] However, there are inconsistencies between developing nations, with a Chinese study by Zhao et al.[16] reporting an average lag time as low as 9 weeks and an Egyptian group reporting 9.9 weeks.[2] When comparing previous Nepalese studies improvements in lag times occurred between 2006 and 2013: In 2006, lag times were reported at between 6-12 months,[9] which improved to 2.5 months in 2013.[4] Surprisingly, our more recent data does not reflect this trend. This increase in latency in presentation is unexpected given the increasing rates of health literacy in Nepal and awareness of retinoblastoma. Nevertheless, it is important to continue to encourage healthcare workers to provide adequate screening and parental education to try and reverse this trend.

To aid recognition and early presentation, adequate descriptions of the presenting symptoms need to be characterised and refined for the Nepali population. The most common presentation was leukocoria, which was seen in approximately two thirds of patients. This compares similarly to previous studies in both developed and developing nations which reported leukocoria as the most common symptoms in between 56 to 80 percent of patients.[2,4,5,8,16] The next most common symptom to prompt medical evaluation in our patient population was proptosis (14%), which aligns with previous Nepali and international research.[4,8] Other studies from developing countries have reported decreased visual acuity[2] and strabismus[5,16] to be the next most common presenting symptoms after leukocoria. This could be attributed to different paediatric examination practices, as well as varying cultural elements between countries, such as literacy rates and aesthetics. Despite this, leukocoria remains the most important symptom of retinoblastoma. Increasing community awareness that the white pupillary reflex being abnormal is crucial to improving the identification of the disease at its early stages and therefore improving prognosis.[15]

In regards to the influence of geography on the incidence of retinoblastoma, previous research in Nepal has shown varied rates of retinoblastoma based on specific regions.[4] Saiju et al. found significantly increased rates of unilateral retinoblastoma from the Hill region and bilateral retinoblastoma from the Terai region. This phenomenon has not been reported in other studies from around the world[16] and our research did not demonstrate this finding. Previous studies showing this difference are likely due to the small sample size-thirty used in Saiju et al.,.[4] Our results showed that unilateral disease presented more commonly (50 vs. 12) which concurs with the majority of epidemiological studies describing rates of retinoblastoma in both developing and developed nations.[2,4-7,17] Bilateral disease usually has a worse prognosis, with secondary tumours often arising after the initial diagnosis[17] and is associated with positive family history.[2] Only 3.23% of our patients showed a positive family history. Furthermore, previous studies in Nepal have shown that consanguinity is seen in parents of patients who present with retinoblastoma, especially the bilateral type.[11] This finding is not replicated in our study as none of our patients were revealed to be the progeny of consanguineous relationships.

Histopathological stage of retinoblastoma is standardised by the "International Classification for Intraocular Retinoblastoma" system. It is a post-surgical method of staging the tumours and correlates to prognosis.[1] We found that the most common histopathological stage was poorly differentiated with optic nerve involvement, identified in 45.16% of children. This was not as dramatic as findings reported in Saiju et al. 2013, who found 92% of patients to have tumour without infiltration. This represents a better prognosis for patients. The primary reason for this difference is likely to be our later lag time. A continued emphasis on the early detection of retinoblastoma can assist in disease

recognition at earlier histopathological stages and assist in preserving sight.

Fig. 1: Clinical presentation with right eye leukocoria. Treated by enucleation and rehabilitation done with custom made prosthesis

The management of retinoblastoma varies between countries, most likely due to differences in access to the appropriate medicine, surgery and facilities. We found in patients whose vision could not be salvaged, they were treated via enucleation (78.38%). The next most common form of treatment was exenteration (5.40%). 40 of our cases received secondary treatment in which chemotherapy was given to 51.35% of treated eyes with high risk characteristics in histopathology. LASER was used in all 12 bilateral cases for non-enucleated eye. Enucleation remains the primary treatment modality in developed countries such as the Singapore and Australia where 60.8% to 94.8% were treated with enucleation, respectively.[5,17] Overall rates of enucleation have been shown to be decreasing in Nepal as previous studies have reported rates to be 100% in 2006 down to 90% in.[4,9] This follows trends in developed countries such as Australia, where Dondey et al.[18] showed rates of enucleation in the state of Victoria to have reduced from 84% to 75% between 1974 and 2001. Unfortunately, the reduction of enucleation rates developing countries appear to be more modest.[19] Clinicians in these countries have been identified as having a low threshold for enucleation, despite the often-higher mortality of these cases when compared to western countries.[5,8,19] This finding can likely be attributed to developing countries having less of a preference for globe preserving surgeries as more advanced chemotherapeutics and other modes of treatment are not as readily available. The continued advances in medical technology in Nepal should lead to more sight and eye preserving management in the future.

The main strength of our present study lies in its large sample size. To date, it is the largest study on retinoblastoma carried out on the Nepalese population. With a larger sample, our study can make more statistically powerful inferences based on the data obtained. This will hopefully lead to a more accurate and clinically useful description of this rare but important eye disease. Importantly, we were able to show that the most common presenting symptom of this condition is leukocoria. Raised awareness of this symptoms has implications for both health professionals and the general public. A further strength is our large sample size allowed us to clarify that retinoblastoma does not carry a predilection for people in certain geographical regions of Nepal. This information may potentially aid ophthalmology outreach programs in targeting the Hill and the Terai regions for opportunistic screening.

The primary limitation of this present study is the short duration of follow up. Patients were only reviewed every 3 months over a 6-month period. This means that further relapses or metastases may not be detected for this population. Patients who were seen at the 6-month mark to have no reduction in lesion size despite laser and chemotherapy (7.2%) subsequently underwent enucleation. Future studies in this area should seek to follow these patients up longer and assess the long-term feasibility of globe saving treatments in the Nepali population.

This study adds to the growing body of literature detailing the clinical identification of retinoblastoma in developing countries. Given that the treatments for this potentially lethal disease can now be life, eye and vision saving, this research provides an important platform from which clinicians can raise both their own and the public's awareness of the signs and symptoms of this disease. Early detection in developing countries is one of the primary means by which patient outcomes can begin to reflect that of developed nations.

Conflict of Interest: None.

References

1. Shields CL, Shields JA. Basic understanding of current classification and management of retinoblastoma. *Curr Opin Ophthalmol* 2006;17(3):228-34.
2. El Zomor H, Nour R, Alieldin A, Taha H, Montasr MM, Moussa E, et al. Clinical presentation of intraocular retinoblastoma; 5-year hospital-based registry in Egypt. *J Egypt Natl Canc Inst* 2015;27(4):195-203.
3. Krishna SM, Yu GP, Finger PT. The effect of race on the incidence of retinoblastoma. *J Pediatr Ophthalmol Strabismus* 2009;46(5):288-93.
4. Saiju R, Moore G, Shrestha U, Shrestha M, Ruit S. Retinoblastoma: geographic distribution and presentation at

a tertiary eye care centre in Kathmandu, Nepal. *Nepalese J Ophthalmol* 2013;5(2):169-76.
5. Lim FP, Soh SY, Iyer JV, Tan AM, Swati H, Quah BL. Clinical profile, management, and outcome of retinoblastoma in singapore. *J Pediatr Ophthalmol Strabismus* 2013;50(2):106-12.
6. Kazadi Lukusa A, Aloni MN, Kadima-Tshimanga B, Mvitu-Muaka M, Gini Ehungu JL, Ngiyulu R, et al. Retinoblastoma in the democratic republic of congo: 20-year review from a tertiary hospital in kinshasa. *J Cancer Epidemiol* 2012;2012:920468.
7. Broaddus E, Topham A, Singh AD. Survival with retinoblastoma in the USA: 1975-2004. *Br J Ophthalmol* 2009;93(1):24-7.
8. Bowman RJ, Mafwiri M, Luthert P, Luande J, Wood M. Outcome of retinoblastoma in east Africa. *Pediatr Blood Cancer* 2008;50(1):160-2.
9. Saiju R, Thakur J, Karmacharya PC, Shah DN. Retinoblastoma in Nepal: a clinical profile of 30 cases. *Nepal Med Coll J NMCJ* 2006;8(3):171-5.
10. Ben L, Aemero M, Gushchin AG, Moore GH, Rohit S. Clinico-Pathological Patterns of Patients Who Underwent Orbital Exenteration in a Tertiary Eye Hospital of Nepal. *Ethiop J Health Sci* 2016;26(6):543-8.
11. Badhu B, Sah SP, Thakur SK, Dulal S, Kumar S, Sood A, et al. Clinical presentation of retinoblastoma in Eastern Nepal. *Clin Exp Ophthalmol* 2005;33(4):386-9.
12. Kiss S LY, Mukai S. Diagnosis, classification, and treatment of retinoblastoma. international ophthalmology clinical. 2008 spring;2(48):135-47.
13. Owoeye JF, Afolayan EA, Ademola-Popoola D. Retinoblastoma-a clinico-pathological study in Ilorin, Nigeria. *Afr J Health Sci* 2006;13(1):117-23.
14. Butros LJ, Abramson DH, Dunkel IJ. Delayed diagnosis of retinoblastoma: analysis of degree, cause, and potential consequences. *Pediatr* 2002;109(3):E45.
15. Abramson DH, Beaverson K, Sangani P, Vora RA, Lee TC, Hochberg HM, et al. Screening for retinoblastoma: presenting signs as prognosticators of patient and ocular survival. *Pediatr* 2003;112(6 Pt 1):1248-55.
16. Zhao J, Li S, Shi J, Wang N. Clinical presentation and group classification of newly diagnosed intraocular retinoblastoma in China. *Br J Ophthalmol* 2011;95(10):1372-5.
17. Azar D, Donaldson C, Kalapesi F, Cumming R. Retinoblastoma in New South Wales 1975 to 2001. *J Pediatr Hematol Oncol* 2006;28(10):642-6.
18. Dondey JC, Staffieri S, McKenzie J, Davie G, Elder J. Retinoblastoma in Victoria, 1976-2000: changing management trends and outcomes. *Clin Exp Ophthalmol* 2004;32(4):354-9.
19. Naseripour M. "Retinoblastoma survival disparity": The expanding horizon in developing countries. *Saudi J Ophthal* 2012;26(2):157-61.

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