BUJO CASE REPORTS

Retinoblastoma in Nepal: case report and review

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Abstract

Retinoblastoma often sparks interest because the underlying cancer gene mutation was the first to be identified and cloned. However, apart from its genetic intrigue, the condition illustrates the health disparities between more and less developed countries. We present a case of retinoblastoma in a 6 month old boy who presented with left eye leukocoria and slight proptosis to the Tilganga Institute of Ophthalmology in Kathmandu, Nepal. Urgent left eye enucleation with orbital implant under general anaesthesia was recommended. Histological examination of the left globe revealed gross involvement of the choroid and optic nerve and poorly differentiated tumour cells. The tumour was staged as pT4a in the TNM classification system and 6 cycles of adjunctive chemotherapy were advised. The epidemiology of retinoblastoma between Nepal and developed countries is compared. We propose reasons for the apparent discrepancy between the two settings and identify areas of weakness which can be improved in Nepal.

Keywords: retinoblastoma, leukocoria, enucleation

Introduction

Retinoblastoma is the most common primary intraocular tumour in children and results from mutations in the tumour suppressor retinoblastoma gene (RB1) located on chromosome 13.[1] As per Knudson's Two Hit hypothesis, retinoblastoma only develops when both alleles of RB1 acquire mutations.[1] In the inheritable form of retinoblastoma, the child inherits one altered allele of the RB1 gene from one parent, meaning retinoblastoma will develop if the normal allele becomes mutated.[1] In the sporadic form, the child inherits normal alleles of the RB1 gene from both parents, but mutations are acquired in both alleles after birth.[1] Of historical significance, the retinoblastoma cancer gene was the first to be identified and cloned.[2] Apart from its genetic intrigue, retinoblastoma is an interesting example of the health disparities between more developed and less developed countries. In more developed countries overall survival rates exceed 95%, a success attributable to both early detection and prompt access to enucleation services.[3] As a result, ocular salvage has now become the main concern.[4] However, in less developed countries, retinoblastoma is still a life-threatening disease.[4] If left untreated, retinoblastoma will invade

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locally and metastasize, mostly causing death within 2 years.[1] Survival rates are about 70% in low and middle income countries.[5] We present a case of retinoblastoma in Nepal, and use it to illustrate what is known about the disease in Nepal, as well as to identify areas for potential development in this context.

Case Presentation

A 6 month old boy presented to the outpatient department in the Tilganga Institute of Ophthalmology with a shiny opacity in the left eye, first noticed by his mother 15-20 days ago. There were no other associated symptoms described by his mother, no past medical history of note, and no history of trauma or eye infection. He was not taking any regular medication and had no known drug allergies. There was no family history of note, including no history of retinoblastoma. He was born at term through a normal vaginal delivery and had no post-natal complications.

Clinically, he appeared fit and alert. He fixed and followed a light when shone in his right eye, but did not respond when the light was shone in his left eye. The red reflex was elicited in his right eye, but not in his left. Retinoscopy of the right eye revealed a refractive error of +3.50 dioptres, but the refractive error of the left eye could not be determined. External eye inspection revealed gross leukocoria with slight proptosis in his left eye. Slit lamp examination revealed quiet anterior chambers with normal depth, round and reactive pupils, and clear lenses bilaterally.

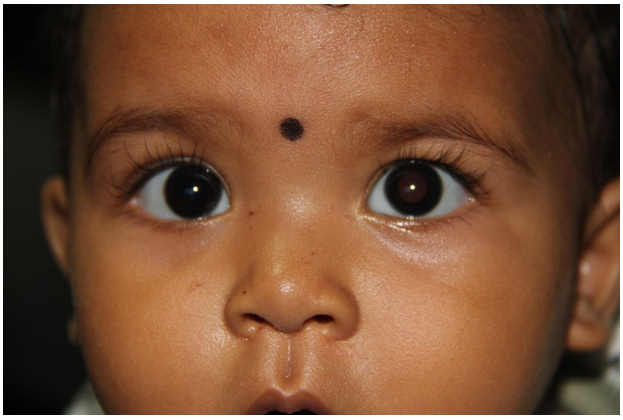

Figure 1 | Leukocoria in the left eye.

Fundus examination was within normal limits in the right eye, but revealed a funnel-shaped retinal detachment in the left eye.

Investigations

B-scan of the left eye demonstrated a hyperechoic shadow with possible areas of calcification. A Computed Tomography (CT) scan of the orbit revealed a heterogenous isodense mass measuring 16 x 12 x 11 mm with dense calcification in the vitreous region in the left eye. The mass occupied two -thirds of the left globe.

Differential Diagnosis

The differential diagnoses of leukocoria include retinoblastoma, congenital cataract, retinopathy of prematurity, toxocariasis, Coats' disease and persistent hyperplastic primary vitreous (PHPV). The normal perinatal history however rules out retinopathy of prematurity. Slit lamp examination revealed clear lenses, ruling out congenital cataract and the lack of inflammatory changes on slit lamp examination ruled out toxocariasis. The characteristics of the mass on ultrasound and CT scan did not correlate with Coats' disease or PHPV. Rather, these characteristic findings on examination and imaging led to a diagnosis of retinoblastoma being confirmed.

Outcome & Follow-up

After discussion, informed parental consent was gained for an urgent left eye enucleation with orbital implant under general anesthesia. The procedure occurred without complications and the globe was sent for histological examination. There were no post-operative complications. A prosthesis was fitted 6 weeks post-operatively for cosmetic improvement.

Histology revealed the tumour size to be 1.8 x 1.8 cm with numerous mitotic figures (5-8/hpf) and a few Homer-Wright cells. The choroid and optic nerve were grossly involved and the tumour cells were poorly differentiated. The tumour was staged as pT4a in the TNM system and as a result, six cycles of adjunctive chemotherapy were advised.

Discussion

In the UK, children with retinoblastoma commonly present with leukocoria (a white pupillary reflex), strabismus, an absent red reflex or nystagmus.[7] The average age at diagnosis is 18 months[8], with 90% of cases diagnosed in patients under 5 years of age.[8] Survival rates for patients with retinoblastoma exceed 90%[9], although extraocular extension, either directly through the sclera or via extension along the optic nerve, is a poor prognostic factor.[10] Globally, the incidence of retinoblastoma ranges from 3.4 to 42.5 cases per million children younger than 5 years.[11]

There have been three studies which have attempted to characterise retinoblastoma in Nepal. The first study was undertaken by Saiju and colleagues, who looked at 30 patients retrospectively from 1998 to 2000.[12] They found that the median age of presentation was 3.1 years, 77% had unilateral involvement, 43% presented with leukocoria, 33% presented with a fungating mass, and on histopathological examination, 70% had poorly differentiated tumour cells.[12] The second study, conducted by Badhu and colleagues, retrospectively analyzed 43 cases between 1995 to 2002 and found that the median age of presentation was 3.04 ± 1.80 years, with 91% of cases being unilateral, 40% presenting with proptosis due to orbital extension, 30% presenting with leucokoria and, on histopathological examination, 42% had optic nerve infiltration.[13] The final, most recent study by Saiju and colleagues examined 30 patients between 2004 and 2008.[14] They found that the median age of presentation was 2.5 ± 1.6 years, 60% of cases were unilateral, 80% presented with leukocoria, 40% presented with a red eye, 20% presented with proptosis and on histopathological examination, 54% had poorly differentiated tumour cells and 38% had optic nerve involvement.[14] However, as a comparison, a retrospective histopathological analysis done at Will's Eye Institute found 40.7% of 297 eyes were classified as poorly differentiated and 38.7% had some degree of optic nerve invasion.[15] These studies together suggest that compared to developed countries, retinoblastoma in Nepal presents later on with more unusual presenting complaints (particularly with fungating mass and proptosis) and has a slightly higher proportion of poorly differentiated tumour cells and optic nerve involvement. It could perhaps be suggested however, on the basis of these three studies, that there is a possible trend of improvement with a declining median age at presentation, more typical presenting features and a declining proportion of poorly differentiated tumour cells and optic nerve involvement. These studies are notably limited in their power given the small sample size, the sampling of only patients who presented to tertiary hospitals in major cities and the lack of histopathological sampling for all patients. Thus, broad trends have to be interpreted carefully and carry questionable validity.

Consideration should be given as to the many factors which could account for later detection of retinoblastoma in Nepal, such as poor awareness of ocular tumours, cultural misunderstandings of important presenting signs and poor access to appropriate eye care services. Furthermore, in contrast to more developed countries, genetic counseling rarely occurs in Nepal due to limited resources. Potentially, access to genetic analysis services could allow for early detection of familial retinoblastoma cases.[16] Indeed, a recent analysis revealed that 83% of patients with bilateral retinoblastoma were from the Terai region and the ratio of unilateral to bilateral cases of retinoblastoma was 1:2 in the lower plains of the Terai region.[14] Since bilateral retinoblastoma cases are usually inherited, Saiju and colleagues hypothesized that the high prevalence could be because of geographical isolation and consanguinity, making genetic testing a useful resource.[14]

Once detected, factors influencing the survival rate of retinoblastoma in developing countries like Nepal include poor access to specialist and multidisciplinary treatment services, treatment compliance, as well as poor education and socioeconomic conditions.[17,18] Improvements in these complex areas are difficult to tackle due to social and

Table 1| The International Classification of Retinoblastoma.[19]	
A (Very Low Risk)	▪ Tumours ≤ 3 mm, confined to retina, located ≥ 3 mm from fovea and ≥ 1.5 mm from optic nerve. ▪ No vitreous or subretinal seeding.
B (Low Risk)	▪ Tumours not in Group A. ▪ A small cuff of subretinal fluid ≤ 3 mm from base of tumour is allowed. ▪ No vitreous or subretinal seeding.
C (Moderate Risk)	▪ Tumours are discrete. ▪ Subretinal fluid involving up to 1 quadrant of the retina. ▪ Focal vitreous or subretinal seeding extending ≤ 3 mm from the tumour.
D (High Risk)	▪ Massive, nondiscrete tumour. ▪ Subretinal fluid involving up to total retinal detachment. ▪ Diffuse vitreous or subretinal seeding
E (Very High Risk)	▪ One or more of the following: - Tumour anterior to anterior vitreous face - Tumour touching lens - Diffuse infiltrating retinoblastoma - Neovascular glaucoma - Massive intraocular haemorrhage - Aseptic orbital cellulitis - Phthisis bulbi

political barriers. At the clinical level however, the recent International Classification of Retinoblastoma (ICRB) (Figure 2)[19] could help ophthalmologists treat their retinoblastoma patients. This framework goes someway to replacing the traditional Reese-Ellsworth classification of intraocular tumours, which was developed to predict the likelihood of preserving vision using external beam radiotherapy (EBRT).[20] However, with the advent of other effective treatment modalities such as chemotherapy, laser photocoagulation, cryotherapy and brachytherapy, the ICRB is better at predicting those likely to be cured without enucleation or external EBRT[21] and takes into account high-risk histopathology.[22] Thus, clinicians can explore eye salvaging options or counsel patients earlier about the need for postoperative systemic therapy.

Conclusion

Although a rare disease, retinoblastoma is a condition that exhibits variation in clinical features, histological evidence and prognosis around the world. In Nepal, patients present at an older age with more unusual presenting complaints when compared to developed countries. Many factors may contribute to this disparity such as poor awareness about ocular tumours, cultural misunderstandings of important presenting signs, poor access to appropriate eye care, genetic and multidisciplinary services, poor treatment compliance and poor socioeconomic conditions. ■

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References

1. Johns Hopkins University. Online Mendelian Inheritance in Man (OMIM). Baltimore: John Hopkins University, 2014. Available from: http://omim.org/entry/180200 (accessed 15 June 2014).
2. Abramson DH. Retinoblastoma in the 20th Century: Past Success and Future Challenges The Weisenfeld Lecture. *Investigative Ophthalmology & Visual Science* 2005;46(8):2684-2691.
3. Chantada GL, Luna-Fineman S, Qaddoumi I et al. Retinoblastoma in Developing Countries. In: Retinoblastoma. US: Springer 2010:133-141.
4. Rodriguez-Galindo C et al. Retinoblastoma: one world, one vision. *Pediatrics* 2008;122(3):763-770.
5. Melamud A, Palekar R, Singh A. Retinoblastoma. *American Family Physician* 2006;73(6):1039-1044.
6. Dimaras H, Kimani K, Dimba EA et al. Retinoblastoma. *Lancet* 2012;379(9824):1436-46.
7. Balmer A, Zografos L, Munier F. Diagnosis and current management of retinoblastoma. *Oncogene* 2006;25(38):5341-5349.
8. Massachusetts Eye and Ear Infirmary. Retinoblastoma. Massachusetts: Massachusetts Eye and Ear Infirmary, 2014. Available from: http://www.djo.harvard.edu/site.php?url=/patients/pi/436 (accessed 15 June 2014).
9. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. Bethesda, MD: National Cancer Institute. http://seer.cancer.gov/ (accessed 15 June 2014).
10. Stannard C, Lipper S, Sealy R et al. Retinoblastoma: correlation of invasion of the optic nerve and choroid with prognosis and metastases. *British Journal of Ophthalmology* 1979;63(8):560-570.
11. Edelman E, Belfort RN, Fu EX, et al. Genetics of Retinoblastoma. In: Genetic Diseases of the Eye. Oxford: Oxford University Press 2011:828.
12. Saiju R, Thakur J, Karmacharya PC et al. Retinoblastoma in Nepal: a clinical profile of 30 cases. *Nepal Medical College Journal* 2006;8 (3):171-5.
13. Badhu B, Sah SP, Thakur SK et al. Clinical presentation of retinoblastoma in Eastern Nepal. Clinical & Experimental *Ophthalmology* 2005;33(4):386-9.
14. Saiju R, Moore G, Shrestha U et al. Retinoblastoma: geographic distribution and presentation at a tertiary eye care centre in Kathmandu, Nepal. *Nepal Journal of Ophthalmology* 2013;5(10):169-176.
15. Eagle, RC Jr. High-Risk Features and Tumor Differentiation in Retinoblastoma: A Retrospective Histopathologic Study. *Archives of Pathology & Laboratory Medicine* 2009;133(8):1203-1209.
16. Chantada GL, Dunkel IJ, Qaddoumi I et al. Familial retinoblastoma in developing countries. *Pediatric Blood & Cancer* 2009;53(3):338-342.
17. Chantada GL, Qaddoumi I, Canturk S et al. Strategies to manage retinoblastoma in developing countries. *Pediatric Blood & Cancer* 2011;56(3):341-348.
18. Chantada GL, Fandiño A, Manzitti J et al. Late diagnosis of retinoblastoma in a developing country. *Archives of Disease in Childhood* 1998;80:171-174.
19. Murphree AL. Intraocular retinoblastoma: the case for a new group classification. *Ophthalmology Clinics of North America* 2005;18(1):41-53.
20. Al-Mesfer S. International Classification and Management of Retinoblastoma. *Saudi Journal of Ophthalmology* 2006;20(3):161-162.
21. Shields CL, Mashayekhi A, Au AK et al. The International Classification of Retinoblastoma predicts chemoreduction success. *Ophthalmology* 2006;113(12):2276-80.
22. Kaliki S, Shields CL, Rojanaporn D et al. High-risk retinoblastoma based on international classification of retinoblastoma: analysis of 519 enucleated eyes. *Ophthalmology* 2013;120(5):997-1003.

LEARNING POINTS

- Retinoblastoma in Nepal presents later and with more unusual symptoms compared to developed countries.
- Bilateral retinoblastoma is usually inherited and a high proportion of bilateral retinoblastoma was recently identified in the Terai region in Nepal.
- The International Classification of Retinoblastoma (ICRB) can be a useful tool for ophthalmologists as it is able to predict those likely to be cured without enucleation or external beam radiotherapy (EBRT) and those with high-risk histopathology.