Time to tumour detection in familial retinoblastoma patients: a retrospective study

Njambi L[1], Dimaras H[2,3,4,5], Gallie BL[3,4,6], Kimani K[1]

[1]Department of Ophthalmology, University of Nairobi / Kenyatta National Hospital, Kenya
[2]Department of Human Pathology, University of Nairobi, Kenya
[3]Department of Ophthalmology & Vision Sciences, The Hospital for Sick Children, Toronto, ON, Canada
[4]Department of Ophthalmology & Vision Sciences, Faculty of Medicine, The University of Toronto, Toronto, ON, Canada
[5]Division of Clinical Public Health, Dalla Lana School of Public Health, The University of Toronto, Toronto, ON, Canada
[6]University Health Network

Corresponding author: Dr Lucy Njambi, Department of Ophthalmology, University of Nairobi, PO Box 19676 code 00202, Nairobi, Kenya. Email: drnjambi@yahoo.com

ABSTRACT

Background: Screening in familial retinoblastoma through regular fundus examination and molecular genetic testing, is recommended to improve prognosis in terms of vision, globe sparing and save life. At The Hospital for Sick Children (SickKids) fundus screening and genetic testing is done in all patients with familial retinoblastoma, while in Kenya there is no formalized screening protocol and genetic testing is not readily available.
Objectives: To determine the mean time to first tumour detection, tumour characteristics and outcome in familial retinoblastoma patients seen at SickKids, Toronto, Canada and Kenyatta National Hospital (KNH), Nairobi, Kenya.
Design: Retrospective descriptive study.
Subjects: Familial retinoblastoma patients at SickKids from July 1, 1993 to September 30, 2013, for KNH, upto when all the medical files could be retrieved. Data collected included patient demographics, disease characteristics, treatment course and outcomes.
Results: A total of 32 patients were reviewed; 20 (63%) were from SickKids and 12 (37%) from KNH. SickKids patients were all bilateral (20/20, 100%), compared to 7/12 (58%) of KNH. The mean time to detection of first tumour was 3.8 months from birth for SickKids and 25 months for KNH. Tumours were diagnosed at birth in 13/40 (33%) of eyes at SickKids while none at KNH. At SickKids most eyes were IIRC Group A (17/34, 43%) or Group B (15/34, 38%). None of the patients had extraocular disease. At KNH, affected eyes were at more advanced stage: IIRC Group D (8/24, 33%) and E (4/24, 17%) with 4/24 (17% eyes) having extraocular disease. All patients were treated using focal therapy at SickKids, (96% had laser photocoagulation). Only 2 (5%) patients had enucleation, while at KNH, all patients had enucleation, (unilateral or bilateral); with half of them receiving additional chemotherapy. At SickKids, 75% of salvaged eyes had vision between 20/20 and 20/60, with 8% having vision less than 20/200. In two eyes (5%) vision was assessed as central, steady and maintained. At KNH, 62.5% of the salvaged eyes had vision reported as fixing and following light, two eyes (25%) had vision better than 20/80. In one eye (12.5%), vision was perception of light.
Conclusion: Early diagnosis and better outcomes were observed at SickKids familial retinoblastoma compared to KNH.
Recommendation: Develop a screening protocol at KNH for familial retinoblastoma through fundus examination and genetic counseling and testing.

Key words: Retinoblastoma, Familial, Genetics, Tumour detection

INTRODUCTION

Retinoblastoma is the commonest malignant intraocular tumour in childhood. It occurs in heritable and non-heritable forms. In 10% of the cases, there is a positive family history[1,2]. Where there is a family history, screening, through regular fundus examination and molecular genetic testing, is recommended in order to improve prognosis in terms of vision, globe salvage and saving life[3,4]. Opinion on optimal screening timings is varied and evidence on screening practice is scarce[5,6].

Retinoblastoma has a high cure rate if detected and treated early when the tumour is still contained in the eye[7]. Eyes with large tumours are at risk of spreading outside the eye, staged by the International Intraocular Retinoblastoma Classification (IIRC) as Group E, are

treated by enucleation[7]. Salvage of useful vision and the eye is possible with small to moderate tumours (IIRC Groups A to D) by use of various treatment modalities, including chemotherapy, radiotherapy, cryotherapy and laser photocoagulation. Mortality is very high if the disease has spread outside the eye despite treatment through chemotherapy and radiotherapy[8,9].

At The Hospital for Sick Children (SickKids), Toronto, children in families with a history of retinoblastoma undergo genetic testing to confirm or rule out the causative retinoblastoma mutation. For those confirmed to carry the familial mutation, or those where genetic testing is not possible / inconclusive, regular fundus screening is performed to detect tumour at its earliest stage. In Kenya, at Kenyatta National Hospital, the national centre for treatment of retinoblastoma, there is no screening protocol for familial retinoblastoma, and genetic testing is not available locally.

This study aims to provide evidence in formulating a screening protocol in Kenya for children with positive family history of retinoblastoma based on the optimal time of examination to detect tumours early when local treatment is possible. The specific objectives of the study were to determine the mean time when tumours are detected, tumour characteristics and outcome in familial retinoblastoma patients seen at The Hospital for Sick Children (SickKids), Toronto, Canada and Kenyatta National Hospital (KNH), Nairobi, Kenya

MATERIALS AND METHODS

Study design and purpose: This was a retrospective descriptive study. The purpose was to document the time of first tumour detection in familial retinoblastoma patients. Ethical approval was received from the respective ethics review bodies at the University of Nairobi and The Hospital for Sick Children.

*Inclusion criteria***:** The study population included all cases of familial retinoblastoma seen in the last 20 years (July 1, 1993 to September 30, 2013, inclusive). Familial retinoblastoma was defined as any retinoblastoma patient with a first-degree relative affected by retinoblastoma.

Data collection: The data collected included patients demographics, disease characteristics (e.g. International Intraocular Classification for Retinoblastoma (IIRC) group of each eye[10], cTNM staging for retinoblastoma version 7 (AJCC, 2010), date first tumour was detected in each eye, and the location of the tumours in the eyes), genetic testing results, treatment course, date of last follow-up and outcomes (e.g. visual and life outcomes). Where the staging was not indicated in the records, clinical notes, drawings, laboratory investigations and imaging reports were used to stage the tumours, where possible.

RESULTS

Study population: Records from 32 patients met inclusion criteria: 20 patients were from SickKids and 12 from KNH. The SickKids patients were all bilateral (20/20, 100%), compared to 58% (7/12) of KNH patients (Table 1). Five KNH patients (42%) were unilateral by the time of last follow up.

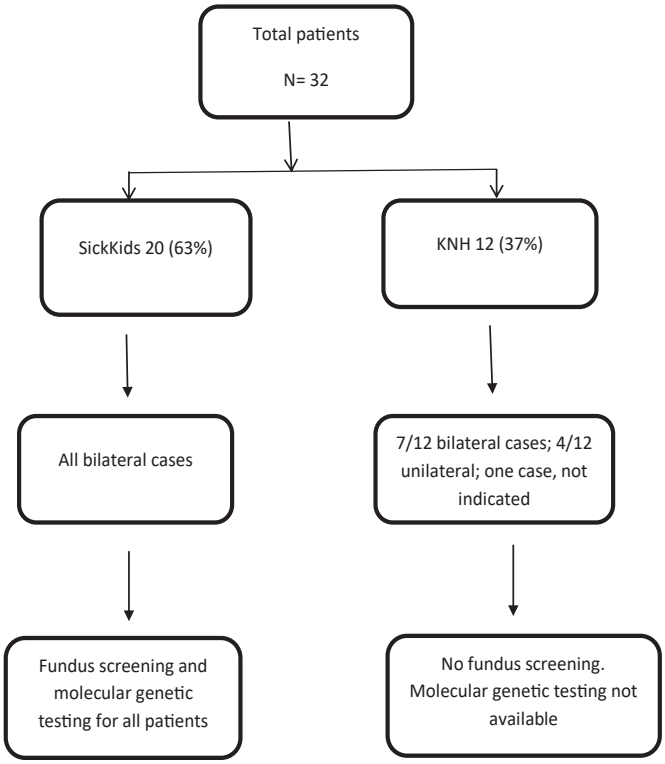

Figure 1: Patients demographics

Timing of tumour detection: Tumours were diagnosed at birth in 33% (13/40) of eyes at SickKids while none of the cases were diagnosed at birth at KNH. The mean time to detection of first tumour was 3.8 months from birth (range 0.1 – 12.4 months) for SickKids and 25 months from birth (range 4 – 61 months) for KNH (Table 1). All KNH patients had tumour at first clinic visit, whereas six SickKids patients had unaffected eyes at first visit, monitored frequently and closely to observe and treat tumours as they developed.

Table 1: Time interval to tumour detection

	Study site	
Time to tumour detection (Months)	SickKids	KNH
Mean	5.3	24
Minimum	0 (birth)	3
Maximum	31	60
Mean time to first tumour detection	3	unknown
Tumour present at birth	Yes 7/20 (35%) No 13/20 (65%)	unknown

Disease characteristics: Eyes of SickKids patients tended to be diagnosed at the lower end of the IIRC spectrum: most eyes were IIRC Group A (17/34, 43%) or Group B (15/34, 38%). None of the patients had extraocular disease (Figure 2). Six eyes (15%) were unaffected at presentation, but later developed tumours.

At KNH, affected eyes tended to be at more advanced stage: IIRC Group D (8/24, 33%) and E (4/24, 17%). Extraocular disease was observed 4/ 24 (16.7% eyes). Staging could not be determined in 6 eyes because of incomplete records.

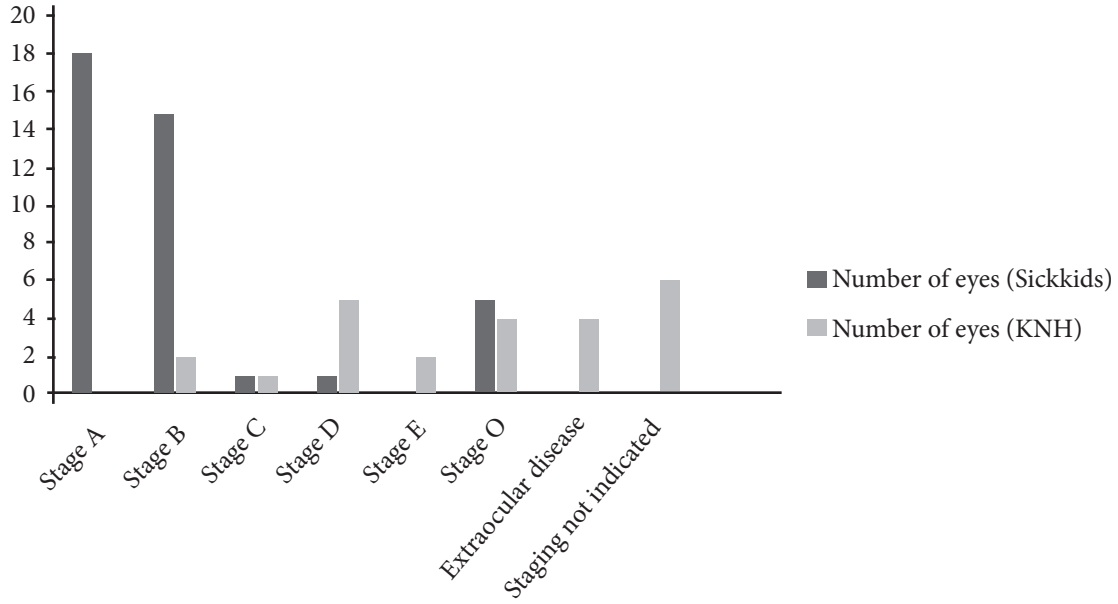

Figure 2: Disease characteristics

Tumour size and location: For the SickKids patients, tumours were evenly distributed in the posterior pole, mid and far periphery, with a slightly higher number in the mid periphery. The tumours were multifocal in 16/20 (80%) of patients, while 4/20 patients (20%) had only one tumour in each eye.

At KNH, most tumours were found in the posterior pole as single large mass. This could be due to the late presentation, in which case multifocal tumours merge and occupy most of the eye thus obscuring the precise location. All the tumours where size was indicated at KNH (23.5%) were larger than 3mm.

Table 2: Tumour location and size

		Study centre			
		SickKids		KNH	
		No. of tumours	(%)	No. of tumours	(%)
Tumour location	Posterior pole	36	28.8	8	50
	Mid periphery	52	41.6	0	0
	Far periphery	37	29.6	0	0
	Details not available	0	0	8	50
Tumour size	≤ 2 Disc diameters	111	88.8	0	0
	> 2 Disc diameters	14	11.2	2	12.5
	Not indicated	0	0	14	87.5

Molecular genetic testing: All patients at SickKids had molecular genetic testing done to identify the familial RB1 gene mutation. Almost half of the patients (9/20, 45%) had the testing done while *in utero* through amniocentesis (Figure 1). None of the patients at KNH had molecular genetic testing done, due to high cost of international testing and no availability of local testing.

Treatment modalities and outcome: At SickKids, all patients were treated using focal therapy, with majority (96%) having laser photocoagulation. Only two (5%) patients underwent enucleation, in comparison to KNH where all patients had enucleation, whether unilateral or bilateral; with half of them receiving additional chemotherapy.

In terms of visual outcome, 75% of salvaged eyes at SickKids had vision between 20/20 and 20/80, with 8% having vision less than 20/200. Out of these, two eyes had perception of light. In two eyes (5%) vision was assessed as CSM (Central, Steady and Maintained). At KNH, 62.5% of the salvaged eyes had vision reported as FFL (Fixing and Following Light), two eyes (25%) had vision better than 20/80. In one eye (12.5%), vision was perception of light.

Table 3: Treatment modalities and outcome

	SickKids		KNH	
	No.	(%)	No.	(%)
Total patients	20		12	
Outcome				
Alive	20	100	9	75.0
Dead	0	0	2	16.7
Unknown	0	0	1	8.3
Total eyes	40		24	
Treatment modalities				
Focal only	26	65	1	4.2
Chemoreduction + Focal	14	35	1	4.2
Enucleation	2	10	16	66.7
Unilateral	2	100	12	75
Bilateral	0	0	4	25
EBRT	0	0	1	4.2
Chemo for high risk pathology	0	0	6 patients	50%

Table 4: Visual outcome

	Study centre			
	SickKids		KNH	
Visual acuity	No. of salvaged eyes (36/40)	(%)	No. of salvaged eyes (8/24)	(%)
20/20- 20/80	27	75	2	25.0
<20/80 -20/200	2	5.6	0	0
<20/200	3	8.3	1	12.5
FFL	0	0	5	62.5
CSM	2	5.6	0	0
Not indicated	2	5.6	0	0

DISCUSSION

Late presentation in retinoblastoma in Kenya, including familial cases, is common[11]. Our results confirmed this, indicating that retinoblastoma patients at KNH are diagnosed late despite a known family history compared to SickKids.

It is known that age at presentation has a bearing on the outcome and prognosis of retinoblastoma in familial cases because having germline mutation results in earlier onset of the disease with a higher possibility of bilateral and multifocal disease[9]. Timely molecular diagnosis of *RB1* mutations enables earlier treatment, lower risks and better health outcomes for patients with retinoblastoma. It also empowers families to make informed family planning decisions and costs less than conventional screening. Health care savings continue to accrue as children in subsequent generations avoid unnecessary examinations and anaesthesia[12]. An evaluation of the cost of molecular genetic testing versus conventional screening showed that the molecular route costs fourfold less compared to conventional screening for a prototypical family with retinoblastoma[13].

At SickKids screening commenced soon after birth of familial patients. For some, genetic testing to identify the familial mutation was performed prenatally; results were available before birth, with screening for new tumours taking place as soon as a child with positive genetic testing is born. At KNH routine screening of patients with family history is not consistent, and genetic testing for patients at risk is not readily available.

Those whose molecular testing was done (SickKids) had earlier diagnosis, less involved tumour presentation, less invasive treatment modalities, better visual outcomes, higher rate of globe salvage and no mortality. At KNH, 17% (2/12) patients died, despite a known family history; they presented late, with more advanced stage of disease. Reasons why familial retinoblastoma patients do not get seen promptly may be varied: perhaps families don't know risks because they were not told; they may have been told about risks but did not understand; or they may know and understand risks but other challenges prevent them from accessing early screening[14, 15].

Prompt screening for familial retinoblastoma has been shown to lead to better visual outcomes; for example, in Netherlands where 73.5% of the eyes had visual acuity between 20/20 and 20/40; and 26.5% had vision between 20/200 and light perception[3]. This is consistent with our findings from the SickKids cohort.

The treatment of choice is also dependent on the stage of presentation of the retinoblastoma. In early stages as noted in the SickKids patients, focal therapy has a high cure rate and globe salvage as opposed to late stage as observed at KNH where enucleation was inevitable and systemic treatment was added as adjunct to save life.

An interesting finding was that no unilateral familial cases were observed in the SickKids cohort, while 41% remained unilateral until last follow-up in the KNH cohort. In most familial cases of retinoblastoma, penetrance is nearly 100%, resulting in bilateral disease. There are however some rare exceptions,

the so called low-penetrance retinoblastoma families. Families with unaffected carriers (that is reduced penetrance), also most often show reduced expressivity. Instead of bilateral disease, some patients have only unilateral retinoblastoma[15]. Thus, while it is possible to observe unilateral familial retinoblastoma, it would not be as many as were observed in the KNH cohort; for example, in the Netherlands study of familial retinoblastoma, 11.7% of the patients had unilateral disease[3]. It is possible that some KNH patients might have later developed tumours in the fellow eye later after loss to follow up.

Indeed, the major limit in our study was the low patient numbers at KNH. One might have expected KNH to have the higher number of patients, considering about 90 new cases of retinoblastoma are seen each year compared to 20 cases at SickKids. However, at KNH loss to follow up is high, and reliable records of up to only 7 years could be retrieved. The higher patient numbers included from SickKids were attributable to more reliable and complete medical records. There was also a possibility some KNH patients with a positive family history of retinoblastoma were excluded from the study due to omission of the information from their medical records, as family history was recorded inconsistently. There may also be fewer familial cases of retinoblastoma in Kenya due to higher mortality from retinoblastoma, resulting in fewer survivors that are able to start families.

We suggest that early diagnosis and survival in familial retinoblastoma at KNH can be markedly improved by taking complete family history, and performing routine fundus screening and genetic testing. We plan to develop a screening protocol at KNH for familial retinoblastoma through fundus examination and genetic counseling and testing.

ACKNOWLEDGEMENTS

The authors wish to thank Drs M Bore and I Makite for their assistance. LN was supported with a fellowship at The SickKids Hospital Toronto, from the Eye Cancer Foundation (New York, NY, USA).

Conflict of interest statement: The authors declare that there is no conflict of interest regarding the publication of this article.

Financial disclosure(s): The authors have no proprietary or commercial interest in any materials discussed in this article.

REFERENCES

1. Castéra L, Sabbagh A, Dehainault C, Michaux D, Mansuet-Lupo A, Patillon B, *et al*. MDM2 as a modifier gene in retinoblastoma. *J Natl Cancer Inst* [Internet]. 2010 Nov 4;**102**(23):1805–8. Available from: https://doi.org/10.1093/jnci/djq416.
2. Aguirre Neto JC de, Antoneli CBG, Ribeiro KB, Castilho MS, Novaes PERS, Chojniak MMM, *et al*. Retinoblastoma in children older than 5 years of age. *Pediatr Blood Cancer* [Internet]. 2007; **48**(3):292–295. Available from: https://doi.org/10.1002/pbc.20931.
3. Imhof SM, Moll AC, Schouten-van Meeteren AY. Stage of presentation and visual outcome of patients screened for familial retinoblastoma: nationwide registration in the Netherlands. *Br J Ophthalmol.* 2006; **90**(7): 875-878.
4. Moll AC, Imhof SM, Meeteren AY, Boers M. At what age could screening for familial retinoblastoma be stopped? A register based study 1945-98. *Br J Ophthalmol.* 2000; **84**(10): 1170-72.
5. Chang CY, Chiou TJ, Hwang B, Bai LY, Hsu WM, Hsieh YL. Retinoblastoma in Taiwan: survival rate and prognostic factors. *Jpn J Ophthalmol.* 2006; **50**(3): 242-249.
6. Diciommo D, Gallie BL, Bremner R. Retinoblastoma: the disease, gene and protein provide critical leads to understand cancer. *Semin Cancer Biol.* 2000; **10**(4): 255-269.
7. Dimaras H, Corson TW, Cobrinik D, White A, Zhao J, Munier FL, *et al*. Retinoblastoma. *Nature Reviews Disease Primers.* 2015: 15021.
8. Leal-Leal CA, Rivera-Luna R, Flores-Rojo M, Juarez-Echenique JC, Ordaz JC, Amador-Zarco J. Survival in extra-orbital metastatic retinoblastoma: treatment results. *Clin Transl Oncol.* 2006; **8**(1): 39-44.
9. Lohmann DR, Gallie BL. Retinoblastoma: revisiting the model prototype of inherited cancer. *Am J Med Genet C Semin Med Genet.* 2004; **129C**(1): 23-28.
10. Linn Murphree A. Intraocular retinoblastoma: the case for a new group classification. *Ophthalmol Clinics North Amer.* 2005; **18**(1): 41-53, viii.
11. Nyamori JM, Kimani K, Njuguna MW, Dimaras H. The incidence and distribution of retinoblastoma in Kenya. *Br J Ophthalmol.* 2012; **96**(1): 141-143.

12. Richter S, Vandezande K, Chen N, Zhang K, Southern J, Anderson J, *et al*. Sensitive and efficient detection of RB1 gene mutations enhances care for families with retinoblastoma. *Am J Hum Genet.* 2003; **72**(2): 253-269.
13. Noorani HZ, Khan HN, Gallie BL, Detsky AS. Cost comparison of molecular versus conventional screening of relatives at risk for retinoblastoma. *Am J Hum Genet.* 1996; **59**(2): 301-307.
14. He LQ, Njambi L, Nyamori JM, Nyenze EM, Kimani K, Matende I, *et al*. Developing clinical cancer genetics services in resource-limited countries: the case of retinoblastoma in Kenya. *Public Health Genomics* [Internet]. 2014; **17**(4):221–227. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25059247.
15. Soliman SE, Racher H, Zhang C, MacDonald H, Gallie BL. Genetics and molecular diagnostics in retinoblastoma - An Update. *Asia-Pacific J Ophthalmol*. 2017; **6**(2):197–207.
16 Lohmann D, Gallie B. Retinoblastoma: Revisiting the model prototype of inherited cancer. *Am J Med Genet C Semin Med Genet.* 2004; **129C**: 23–28.