Magnitude of delay in presentation and management of retinoblastoma patients at the Kenyatta National Hospital, Kenya

Makite I, Kimani K, Njuguna M

Department of Ophthalmology, Faculty of Medicine, University of Nairobi, P.O. Box 19676-00202, Nairobi, Kenya

Corresponding author: Dr. I. Makite. Email: teresamakite@yahoo.com

ABSTRACT

Background: Retinoblastoma is the commonest intraocular childhood malignancy in the world and is curable when detected early. Delay in presentation and management is seen as a major contributor affecting outcome.
Objective: To determine the magnitude of delay in the presentation and management of retinoblastoma patients at the Kenyatta National Hospital.
Methodology: A cross sectional hospital based study done from November 2012 to April 2014 at the Kenyatta National Hospital. Data was collected using a semi structured questionnaire from the parents/guardians of retinoblastoma patients who gave consent.
Results: Ninety-one parents/guardians of 64 patients participated. Sixty point nine percent took more than 5 months from onset of symptoms to presentation at the referral centre while 46.1% took more than 1 month from onset of symptoms to first visit to a health facility. Ten point nine percent of patients took more than 2 weeks before starting definitive management at the referral centre.
Conclusions: Majority of the patients presented late to the referral centre while most of the health care providers referred the patients early. Augmentation of public awareness on retinoblastoma would make the primary caregivers more aware of early symptoms of the disease.

Keywords: Retinoblastoma, Childhood malignancy, Delay, Magnitude, Kenyatta National Hospital

INTRODUCTION

Retinoblastoma is the commonest intraocular childhood malignancy in the world and is curable when detected early. It is a rare tumour with malignant transformation of primitive retinal cells before final differentiation[1].

In developing countries, retinoblastoma is detected at more advanced stages and has a poorer prognosis compared with developed countries[2]. Kenya has an incidence of 1 in 17030 live births, comparable with worldwide incidence of 1:14000 to 1:20000 live births[3]. The mean age at presentation for unilateral disease is 35.9 months and 26 months for bilateral disease in Kenya[3] while in the US the mean ages are 24 months and 12 months respectively[4]. The mean delay in first presentation to a health provider was 6.75 months with 4.5% of the cases reporting within 1 month. A mean delay of 1.69 months was noted after referral[3]. Five years survival rates of less than 50% have been reported in developing countries. This is low as compared to developed countries where survival rates are more than 90% [5].

This study assessed the time taken by primary caregivers of retinoblastoma patients in seeking health care at different stages from onset of the initial symptoms to presentation at the referral centre and subsequent initiation of treatment. To our knowledge, no similar study has been done previously in Kenya.

MATERIALS AND METHODS

A descriptive cross sectional hospital based study at the Kenyatta National Hospital eye ward and eye clinic, was carried out on retinoblastoma parents/guardians from November 2012 to April 2014. Ethical approval was granted from the Kenyatta National Hospital – University of Nairobi Ethics Board. A list of 66 patients admitted with retinoblastoma from January 2012 to September 2013 was made using admission records in the eye ward; contact details of the caregivers were also collected from the admission records; 2 patients had no contact details.

Data was collected using a pretested semi-structured questionnaire, with both open and closed ended questions, from the parents/guardians of the retinoblastoma patients. Hospital records were used to get information on the clinical and histological staging of the disease. Both parents/ guardians were interviewed separately and were also contacted via phone, if not available at the time of the interview.

Delay in presentation and treatment were defined in terms of [6]: (1) *Overall lag time* as timing between onset of symptoms and presentation at the referral centre for definitive management; (2) *Lag 1* from onset of symptoms to first consultation with a health worker (parental delay); (3) *Lag 2* from 1st contact with health worker to point of referral for definitive management (health worker delay); (4) Time interval from referral by the health provider to presentation at the centre for definitive management; (5) Duration from presentation at the referral centre to start of definitive management. Overall lag time of *5 months* and more was taken as delay. Delay from referral by a health worker and presentation at the referral centre of *more than 1 week* was used. Delay in treatment was defined as *more than 2 weeks* from the first presentation at the referral centre to start of definitive management.

Data was analysed using STATA version 11. Descriptive statistics were used to summarise and describe the data. An alpha value of 0.05 was used for all significance tests. All analysis regarding the patient and the caregivers were restricted to the primary caregivers.

RESULTS

In total 64 patients participated in the study with 91 parents/guardians interviewed. Eleven patients had single parents, 27 patients had both parents available and 26 patients had only the available parent interviewed. This was due to various reasons which included refusal to give consent (n=2), out of the country (n=2), not picking their phones (n=8), wrong contact details (n=10). Those who had a deceased child (n=4) due to retinoblastoma consented to only one parent to take part in the study. The male to female ratio amongst the study patients was 1.5:1 (p=0.03); this was statistically significant (Table 1). The median age at onset of symptoms for bilateral disease was 3.5 months (SD 7.76) and 20.5 months (SD 21.0) for unilateral disease. The most common symptoms from the onset were leukocoria (92.2%), redness (34.4%), proptosis (31.3%) and poor vision (23.4%).

The median age at first presentation to the referral centre for bilateral disease was 14.7 months (SD 12.2) and 30.5 months (SD 19.9) for unilateral disease with the mean age for bilateral disease at 23.6 months (SD 14.7) and 43.2 months (SD 18.6) for unilateral disease. The difference was statistically significant (p <0.001) (Table 1).

Table 1: Summary statistics of the study patients (n=64)

Characteristics	No. (%)
Gender	
Male	38 (59.4)
Female	26 (40.6)
Age at 1st presentation to referral centre (months)	
<12	18 (28.1)
12 – 24	17 (26.6)
25 – 36	9 (14.1)
37 – 48	9 (14.1)
49 - 60	6 (9.4)
61 months and above	5 (7.8)
Laterality	
Unilateral	43 (67.2)
Bilateral	21 (32.8)
Family history	
Present	4 (6.3)
Absent	60 (93.7)

The mean time interval between onset of symptoms and first visit to a health facility (lag 1) was 4.7 months (SD 7.2) median of 2 months (range 0.25 -36 months). The mean lag 1 time for those with bilateral disease (n=21) was 2.6 months (SD 5) while for unilateral (n=43) was 5.3 months (SD 6.9).The difference in the means was not statistically significant (p-value= 0.11) (Table 2).

Table 2: Time interval from onset of symptoms to first visit at the health facility (lag 1) (n=64)

Time interval (months)	No. (%)
<1	15 (23.4)
1 – 2	15 (23.4)
2 – 3	7 (10.9)
3 – 4	5 (7.8)
4 – 5	5 (7.8)
5 – 6	2 (3.1)
6 – 9	3 (4.7)
9 – 12	5 (7.8)
>12	7 (10.9)
Total	64 (100)

The mean time interval between first contact with health worker and referral (lag 2) was 1.8 months (SD 2.8), median of 0.5 months (range 0-11months) (Table 3).

Table 3: Time interval from initial contact with health worker to referral (lag 2) (n = 64)

Time interval (months)	No. (%)
<1	34 (53.1)
1 – 2	11 (17.2)
2 – 3	3 (4.7)
3 – 4	3 (4.7)
4 – 5	3 (4.7)
5 – 6	3 (4.7)
6 – 9	2 (3.1)
9 – 12	4 (6.3)
>12	1 (1.6)
Total	64 (100)

The mean delay between referral and presentation at the referral centre was 7.3 weeks (SD 16) and the median delay was 0.5 weeks (range 0.1-77 weeks) (Table 4). The mean overall lag time for those with bilateral disease (n=21) was 7.0 months (SD 1.6) while for unilateral disease (n=43) was 8.5 months (SD 1.3). The difference in the means was not statistically significant (p-value= 0.48).

Table 4: Duration between referral and presentation to referral centre (n=64)

Time interval (weeks)	No. (%)
≤1	41 (64.1)
1 – 2	4 (6.3)
2 – 3	1 (1.6)
3 – 4	5 (7.8)
4 – 8	0 (0)
8 – 12	0 (0)
12 – 16	1 (1.6)
16 – 20	3 (4.7)
20 - 24	1 (1.6)
24 - 52	3 (4.7)
>52	5 (7.8)
Total	64 (100)

* Delay was defined as >1week from referral to presentation to referrral centre.

Mean delay between referral and presentation to referrral centre for unilateral disease was 5.25 weeks (SD 11.7) while for bilateral disease, it was 11.4 weeks (SD 21.8) with p-value of 0.15. The mean overall lag time was 8.1 months (SD 7.8) with a median of 5 months (range 0.4 - 45 months) (Table 5). Out of the 64 patients, 60.9% took more than 5 months from initial symptom to presentation at the referral centre for definitive management (Table 5).

Table 5: Overall lag time (n=64)

Time interval (months)	No. (%)
<1	3 (4.7)
1 – 2	7 (10.9)
2 – 3	10 (15.6)
3 – 4	3 (4.7)
4 – 5	2 (3.1)
5 – 6	7 (10.9)
6 – 9	6 (9.4)
9 – 12	9 (14.1)
>12	17 (26.6)
Total	64 (100)

Table 6: Clinical stage of the disease (n=64)

Stage of the disease	Frequency (%)
Clinical stage at diagnosis	
Extraocular	25 (39.1)
Intraocular	39 (60.9)
Clinical stage at start of treatment	
Extraocular	24 (37.5)
Intraocular∞	38 (59.4)
No treatment given*	2 (3.1)

*1 patient with extra-ocular stage of disease was referred to the neighbouring country for management upon request from the guardian; 1 patient with extra-ocular stage of disease declined admission at the time of the study. ∞1 patient with intraocular disease declined admission initially and came back after the disease had progressed.

The mean time interval before start of treatment was 3.4 weeks (SD 10) with a median of 1 week (range of 0.1-72 weeks) (Table 7).

Table 7: Time interval between presentation to referral centre and start of treatment (n=64)

Time before treatment (weeks)	No. (%)
No treatment given*	2 (3.1)
<1	26 (40.6)
1 – 2	31 (48.4)
2 – 4	1 (1.6)
4 –24	0
24 – 52	2 (3.1)
>52	2 (3.1)
Total	64 (100)

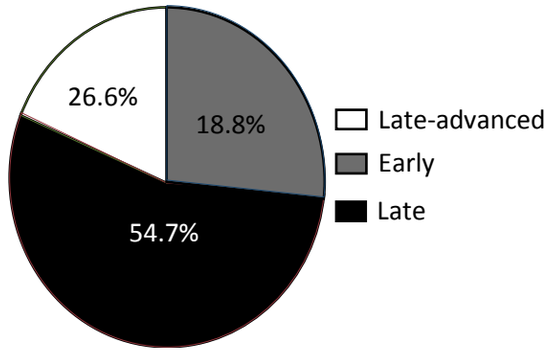
*1 patient declined admission for treatment; 1 patient requested referral to another facility in a neighbouring country

Table 8: Histopathological staging (n=64)

Histopathological staging	Frequency (%)
No enucleation done*	5 (7.8)
pT2-unclassified	2 (3.1)
pT2a	5 (7.8)
pT2b	10 (15.6)
pT3-unclassified	4 (6.3)
pT3a	20 (31.3)
pT3b	11 (17.2)
pT4-unclassified	1 (1.7)
pT4a	3 (4.7)
pT4b	3 (4.7)
Total	64 (100)

*Enucleation was not done due to advanced retinoblastoma. Of these 5, 1 patient was referred to a neighbouring country upon request by the guardian and another declined admission to the hospital

Figure 1: Stage of the disease



DISCUSSION

The median age at onset of symptoms was 3.5 months (SD 7.8) and at first presentation to the referral centre for definitive management was 14.7 months (SD 12.2) for bilateral disease while for unilateral disease, it was 20.5 months (SD 21.0) and 30.5 months (SD 19.9) respectively (Table 1). This shows that patients were brought to the referral hospital 10 months after the initial symptom was noted. Kao *et al*[7] in Taiwan showed a delay of 2.53 months from first detection of symptoms to subsequent formal diagnosis of the disease.

Leukocoria (92.2%) was the commonest symptom from the onset, with proptosis found in 31.3% of the patients. This was similar to studies done in Kenya, Ghana and Malaysia[8 - 10]. In the US, ocular inflammation was at 5% with leukocoria and strabismus being the most common presenting symptoms[5].

The median time between onset of the symptoms to first visit at a health facility *(lag 1)* was 2 months. Goddard *et al*[6] in the United Kingdom found a median lag 1 of 2.5 weeks. This shows that our patients presented late to a health facility. This could be because the initial symptoms of retinoblastoma tend to be painless and, therefore, children may be taken to hospital when they are not able to see well or when they complain of pain.

In our study, the median delay in referral of patients by the health professionals *(lag 2)* was 0.5 months. This is similar to findings by Goddard *et al*[6] in the UK who found the lag 2 median to be 2 weeks. The median delay between referral and presentation at the referral centre was 0.5 weeks. This could be because the health workers explained to the caregivers about the seriousness of the diagnosis and referred to the appropriate facility for definitive management.

The overall delay from onset of symptoms to presentation at the referral centre (overall lag time) had a median of 5 months. Gichigo *et al*[8] found a median time of 10.5 months while Nyamori *et al*[3] found a mean of 6.75 months as the overall duration. This shows a progressive improvement of the overall delay over the years in Kenya. This could be attributed to the awareness campaigns focusing on retinoblastoma in the country[3].

The study found that 73.7% of the patients had a histological staging of pT3 and worse; early disease (pT2a and b) was found in 26.6% of patients. Gichigo *et al*[8] found early disease in 28.3% while Nyamori *et al*[3] found in 26%. Kashyap *et al*[11] in India found 66.4% of enucleated eyes with early disease with focal choroidal, prelaminar involvement and no sclera involvement while 8.6% had advanced disease with residual tumour.

Our study showed that 60.9% of patients took more than 5 months from initial symptoms to presentation at the referral centre and 10.9% of patients took more than 2 weeks before starting treatment. Butros *et al*[12] found 77% of the participants delayed seeking treatment; this was defined as the time from onset of symptoms to presentation to a physician, who subsequently referred the patient to the facility of definitive management.

CONCLUSIONS AND RECOMMENDATIONS

More than 50% of the patients presented late in our study. The longest delay interval was the parental delay, from onset of symptoms to presentation at the first health facility. Most health care providers took a short time to refer the patients to a facility of definitive management. For almost all of the patients, treatment was started within 2 weeks of being admitted to the referral centre.

There is a persistent need for continued medical education to the primary health workers on early detection of retinoblastoma and appropriate referral to an eye care specialist.

Augmentation of public awareness on retinoblastoma, especially in the mother and child health clinics, would allow the primary care givers and primary health workers to be more aware of symptoms of retinoblastoma. This will help reduce the delays that occur as a result of parents' ignorance and delayed referrals by clinicians.

REFERENCES

1. Kanski, J. *Clinical Ophthalmology, A Systematic Approach.* s.l. : Butterworth- Heinemann- Elsevier, 2007. ISBN-13: 978-0-08-044969-2.
2. Jamalia R, Sunder R, Alagaratnam P, Goh P, *et al*. Retinoblastoma registry report - Hospital Kuala Lumpur experience. Supplement A, Kuala Lumpar. *Med J Malaysia*. 2010; **65**: 128 - 130.
3. Nyamori JM, Kimani K, Njuguna MW, Dimaras H**.** The incidence and distribution of retinoblastoma in Kenya*. The Brit J Ophthalmol*. 2012; **96**: 141–143.
4. Ophthalmologists, American Academy of *Ophthalmic Pathology and Intraocular Tumours: Section 4 - BCSC.* Singapore : AAO, 2011 - 2012.
5. Lukusa AK, Aloni MN, Tshimanga BK, Muaka MM, Ehungu JLG, Ngiyulu R. Retinoblastoma in the Democratic Republic of Congo: 20-year review from a tertiary hospital in Kinshasa. Kinshasa. *J Cancer Epidemiol*. 2012; **2012**. Article ID 920468.
6. Goddard AG, Kingston JE, Hungerford JL**.** Delay in diagnosis of retinoblastoma: risk factors and treatment outcome*. The Brit J Ophthalmol*. 1999; **83**: 1320-3.
7. Ling-Yuh Kao, Wei-Wen Su, Ya-Wen Lin**.** Retinoblastoma in Taiwan: Survival and clinical characteristics 1978–2000. *Japanese J Ophthalmol.* 2002; **46**(5): 577-580.
8. Gichigo N, Kariuki M, Kimani K**.** Survival among retinoblastoma patients at KNH, a retrospective audit., Nairobi. *J Ophthalmol Eastern Central and Southern Africa*. 2013; **17**(1): 16 – 19.
9. Essuman V, Ntim-Amponsah CT, Akafo S, Renner L, Edusei L**.** Presentation of retinoblastoma at a paediatric eye clinic in Ghana. *Ghana Med J.* 2010; **44**: 10-15.
10. Menon BS, Alagaratnam J, Juraida E, Mohamed M, Ibrahim H, Naing NN**.** Late presentation of retinoblastoma in Malaysia*. Paediat Blood Cancer*. 2009; **52**(2). 215 – 217.
11. Kashyap S, Meel R, Pushker N, Sen S, Bakhshi S, Sreenivas V, *et al.* Clinical predictors of high risk histopathology in retinoblastoma. wileyonlinelibrary. com*. Paediat Blood Cancer.* 2011, DOI 10.1002/ pbc.23239.
12. Butros LJ, Abramson DH, Dunkel IJ**.** Delayed diagnosis of retinoblastoma: analysis of degree, cause, and potential consequences*. Pediatrics* [Internet]. 2001; **109**(3): e45–e45.