East African Medical Journal Vol. 88 No. 12 December 2011
CLINICO-SURGICAL HISTOPATHOLOGICAL FINDINGS OF RETINOBLASTOMA CASES TREATED AT KENYATTA NATIONAL HOSPITAL
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CLINICO-SURGICAL HISTOPATHOLOGICAL FINDINGS OF RETINOBLASTOMA CASES TREATED AT KENYATTA NATIONAL HOSPITAL

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ABSTRACT

***Background*: Retinoblastoma is a primitive embryonal anaplastic tumour composed of undifferentiated retinal elements. It is the most common primary, intraocular malignancy of childhood. After enucleation of the diseased eye, histopathological findings determine the secondary management of the patient. Histopathological spread of the disease is a major prognostic factor on survival of the patient.**

***Objectives*: To determine the surgical and histopathological findings of retinoblastoma cases treated at the Kenyatta National Hospital between 1st January 2000 and 31st December 2004 and to correlate gross appearance of globe after enucleation, with histopathological report.**

***Design*: Retrospective study.**

***Setting*: Kenyatta National Hospital, Kenya's largest referral and teaching hospital.**

***Subject*: One hundred and sixty patients with clinically diagnosed and/or hystologicaly confirmed retinoblastoma.**

***Results*: The mean duration of symptoms was ten and a half five months (SD 10.7) median eight months. White reflex was most common symptom in 53.3% of cases, orbital swelling in 39.4%, pain and redness in 15%, squint in 5% and 21.9% had other complaints. On examination, leucocoria was found in 38.8% of patients, enucleated sockets 37%, recurrent mass in the socket in 27.5%, proptosis 22.5%, orbital swelling in 20% while only 1.3% of patients had strabismus. Tumour was found to be grossly confined to the eye ball in 23.0% of operated eyes, clinically outside the eye ball in 14.3% of eyes while 12.4% of operated eyes had thickened optic nerves. Histologically, tumour was confined to the eye ball in 30% of operated eyes while tumour involved the optic nerve but resection margin free of tumour in 3% of eyes. Tumour had extended beyond the resection margin of the optic nerve in 21% of cases. Eleven point four percent had choroidal extension and 24% were reported as having extrascleral spread. The sensitivity of the surgeon's finding at surgery, when compared to the histological findings was found to be 69.4% while the specificity was 69.6%. The accuracy was 69.5%.**

***Conclusion*: There was still late presentation of retinoblastoma in our set up that had been found in studies conducted previously. This was confirmed by the histological findings. There was inadequate documentation of surgical findings, poor record management and a non-comprehensive referral system.**

INTRODUCTION

Retinoblastoma is a primitive embryonal anaplastic tumour composed of undifferentiated retinal elements. It is the most common primary, intraocular malignancy of childhood. Retinoblastoma has a worldwide distribution affecting all races. It accounts for 3% of all childhood cancers and occurs in about 1:17,000 live births worldwide and in 1:19,000 live births in Kenya (1,2). No significant sex difference has been noted. Patients present with retinoblastoma within the first year of life in bilateral cases and around two years of age if the tumour is unilateral. However, 8.5% patients are children older than five years at initial diagnosis (3). In Kenya, majority of children (61.4%) were seen in the second and third years of life (unpublished). Majority of retinoblastoma patients in Kenya and other developing countries present late (2,4). Children with bilateral disease

present earlier than those with unilateral disease (5). Retinoblastoma is unilateral in approximately 67% of cases and bilateral in 33% of cases (2,5-7).

In the developed countries, leucocoria is the most common presenting complaint while strabismus is the second most common (6). The clinical picture in developing countries is quite different because of late presentation. While most patients will have leucocoria as the most frequent initial symptom, patients present to the ophthalmologist with proptosis and inflammation (2,4,9). A study conducted in 1985 at KNH found over 90% of the patients presented late, only 10% were amenable to focal methods of treatment (2). Late presentation and metastatic disease are associated with poor outcomes. Late presentation in our setting has been attributed to parents' ignorance, poor referral system and financial constraints (Unpublished).

Histopathologically, retinoblastoma consists of small basophilic cells with large hyperchromatic nuclei and scanty cytoplasm. Many tumours are undifferentiated but varying degrees of differentiation is characterised by formation of rosettes as in Flexner Wintersteiner rosettes, Homer-Wright rosettes and fleurettes. Plentiful rosettes were usually found in those tumours that had not extended beyond the choroid or as far as the resection line of the optic nerve and were, therefore, associated with a good prognosis.

In cases of early tumour detection, there is improved and increased use of more conservative eye sparing treatments. However, enucleation remains a frequent treatment for retinoblastoma. It is indicated for all unilateral tumours that fill over half of the eye or when there are vitreous seeding, rubeosis or optic nerve involvement. It is also performed if chemoreduction fails or a normal fellow eye makes aggressive chemotherapy being a poor choice for treatment': It is useful for diffuse retinoblastoma because of poor visual prognosis and high risk of recurrence with other therapeutic modalities. It is the most common mode of treatment used in Kenyatta National Hospital, Nairobi (2). Due to delays in histopathological reporting, decision making on the subsequent adjuvant management of retinoblastoma patients (where indicated) has on occasion been based on gross appearance of the globe at enucleation. It is therefore important to compare histology reports with the gross appearance of the globe as a retrospective audit of the accuracy of our decision making process.

MATERIALS AND METHODS

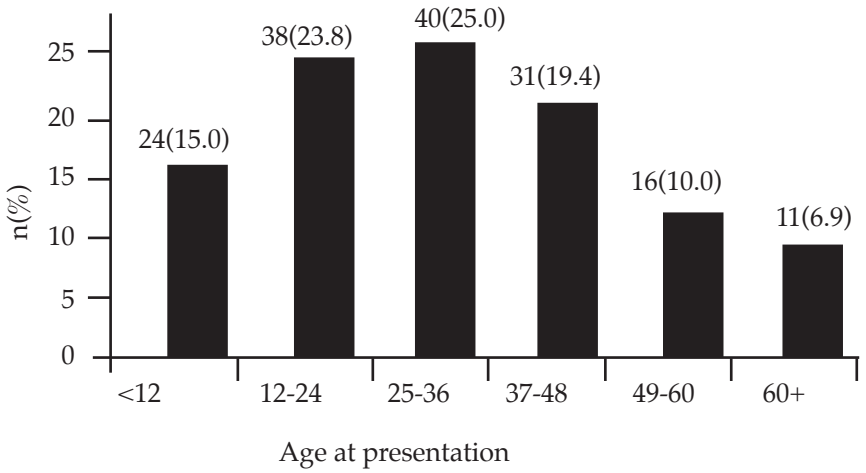
This was a retrospective study conducted at the Kenyatta National Hospital, Kenya's largest hospital. All patients admitted with retinoblastoma at Kenyatta National Hospital in the period between 1st January 2000 and 31st December 2004 and all records of patients with retinoblastoma clinically diagnosed and or histologically confirmed were included. All records of patients whose histopathological report ruled out retinoblastoma were excluded. Approval from the Kenyatta National Hospital's Ethical Board was sought and obtained and patient's records were treated with confidentiality.

All patient records of patients admitted with retinoblastoma in the period January 2000 to December 2004 were retrieved. The International Disease Coding method was applied. Information from the socio-biographical data sheet and or the patient cadex was retrieved and recorded in a questionnaire. The other information that was obtained from patient records was age at presentation, the duration of symptoms, laterality of disease, presenting complaint and ocular findings on examination. Findings at surgery were also recorded, it was indicated whether tumour was within the globe grossly, outside the globe and whether or not the optic nerve was thickened. Histopathology report where available was indicated; was the tumour confined to the globe, was it involving the optic nerve but resection margin free of tumour or was the margin involved, was there extrascleral spread and or cellular differentiation. The data were stored in a computer for analysis. Analysis was carried out using the Statistical Package for Social Scientists (SPSS) Version 12.

RESULTS

A total of 160 patients were included in this study. The distribution by sex, male to female ratio was 1.16: 1 (54 and 46% respectively). The distribution by bilaterality was 67% (108) for bilateral case and 33% (52) for unilateral cases.

Figure 1
Distribution by age at presentation

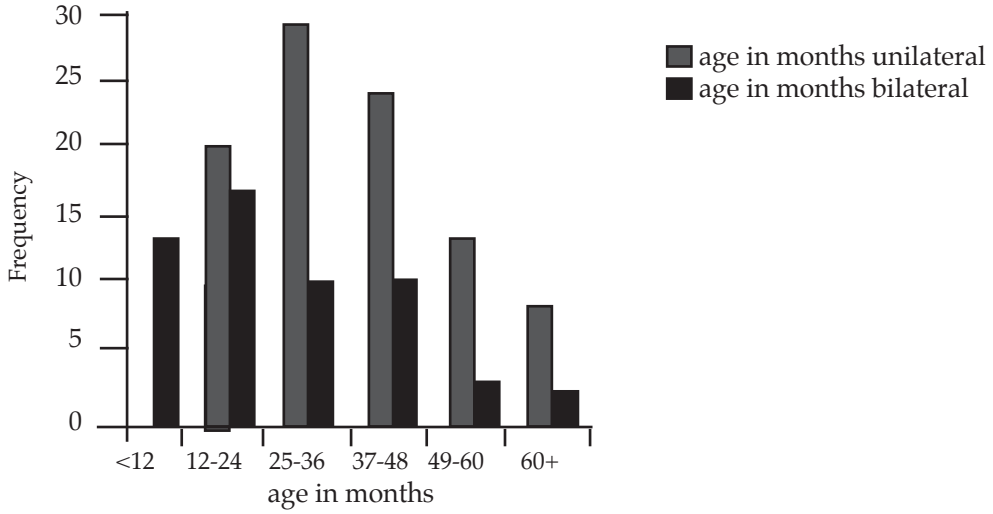


The mean age was 35 months SD 25, median age 33 and a half months, mode 36, and range between 1 and 144 months.

Table 1
Age at presentation: Age in months Vs Bilaterality n=160

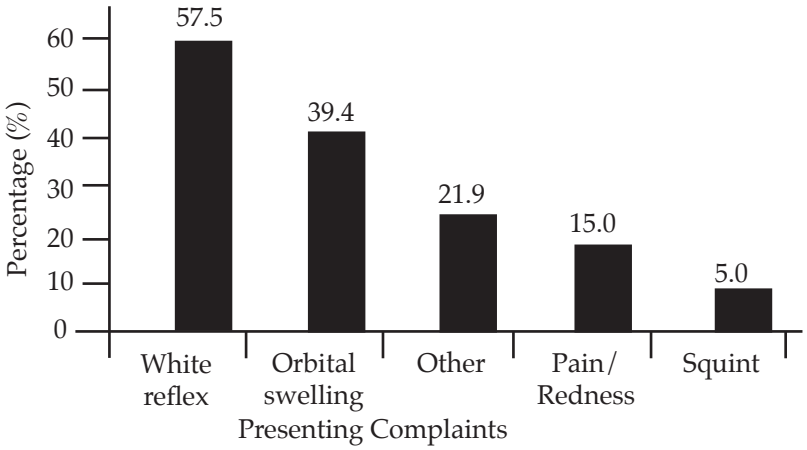
	Bilaterality	
Age in month	Unilateral, n (%)	Bilateral, n (%)
<12	10(41.7)	14(58.3)
12-24	21(55.3)	17(44.7)
25-36	30(75.0)	10(25.0)
37-48	25(80.6)	6(19.4)
49-60	13(81.3)	3(18.8)
60+	9(81.8)	2(18.2)
Total	108(67.5)	52(32.5

Figure 2
Age at presentation: Age in months Vs Bilaterality n=160



The mean age of the unilateral patients was 39.89 months compared to 24.35 months among the bilateral patient; the mean difference was 15.54 with a p-value of less than 0.001.

Figure 3
Presenting Complaints



Other presenting complaints were:
Loss of vision 10
No complaints/Routine EUA 9
Shrunken eyes 7
Itching 5
Tearing/photophobia 4

Table 2
Ocular Findings on Examination

Findings	Frequency	Percentage (%)
Leucocoria	62	38.7
Enucleated	60	37.5
Recurrent Mass	44	27.5
Proptosis	36	22.5
Orbital Inflammation	32	20
Strabismus	2	1.2
Other	10	6.2

Other ocular finding on examination:
Phthisis 7
Lid swelling 2
Nystagmus 1

Table 3
Findings at Surgery n = 212 eyes

Findings	Frequency	Percentage (%)
Tumour within globe grossly	50	23.6
Tumour outside clinic all	31	14.6
Thickened optic nerve	27	12.7
Inadequate Information	12	5.7
Referral with no surgical notes	47	22.2
Surgery not done	50	23.6

50 eyes (23.6%) were not operated for various reasons:
Parent/guardian declined to consent 10
Patients with bilateral disease lost to follow up after first operation 17
Patients with metastatic disease not amenable to surgery (palliative care) 8
Phthisical eyes 7
Tumour treated with sight saving procedures (laser and EBRT) 8

Table 4
Histopathological findings

Histology findings	Frequency	Percentage (%)
Tumour confined to eyeball	48	30
Tumour involving optic nerve but resection margin free	5	3
Tumour involving optic nerve up to resection margin	34	21
Choroidal extension	17	11.4
Extrasceral spread	39	24
Non histology report	38	23.4
Inconclusive reporting on tumour extent	13	8

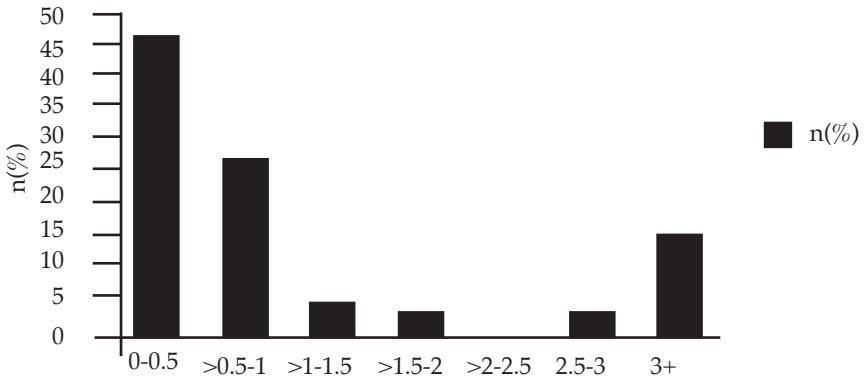
Moderate cellular differentiation was reported in six of the 162 operated eyes. None of the operated eyes was reported as being highly differentiation. Thirteen specimen (8%) were confirmed as having retinoblastoma but the extent of the tumour was not reported.
No histology report was available for 38 of the operated eyes (23.4%). Seventeen of the 162 eyes had choroidal extension of the tumour.

Table 5
Histology versus surgical findings

	Histology		
At surgery	Intraocular	Etraocular	Total
Intraocular	25	10	35
Extraocular	11	23	34
Total	38	33	

The sensitivity of the surgeons' findings at surgery when compared to the histological findings was found to be 69.4% while the specificity was 69.6%. The positive predictive value was 71.4% while the negative predictive value was 67.6%. The accuracy was 69.5%.

Figure 4
Duration between surgery and histology reporting



Mean was two and a half months with a standard deviation of 4.2, mode was 1 month, 48% of histology were reported within two weeks of surgery. The duration ranged between three days and four months.

DISCUSSION

No significant sex differences were found in this study. The distribution of male to females was found to be 1: 1.6 which was quite similar to the ratio of 1: 1.3 found in the study by Khan *et al* (1985) done in Kenya (unpublished).

The distribution by bilaterality was found to be 67% being unilateral cases and 33% for the bilateral cases. This is similar to studies previously in the developed world (6). In Kenya, previous studies found the distribution to be approximately 63% being unilateral and 37% bilateral (2).

Only 15% of patients presented in the first year compared to 23.8 and 25% who presented in the second and third year respectively (Figure 1). The mean age at presentation were 35 months (SD 25) with a median age of 33 and half months and ranging from one to one hundred and fourty four months. These are similar to findings done previously in Kenyatta National Hospital (2). Compared to studies done in developed countries and even developing countries like India and Turkey this is very late presentation (5,7). This late presentation was found to be due to parents' ignorance of the value of early medical intervention when symptoms are noted in the affected children, poor referral system and financial constraint that may have deterred parents from traveling to referral centres (unpublished). KNH is a national referral centre so the patients that present here usually will have been seen in one or two peripheral centres so time may have been lost in the referral system. The mean age at presentation of unilateral patients was 39 to 89 months compared to 24 to 35 months for the bilateral disease and the difference was statistically significant (Figure 2). The bilateral patients presented earlier probably because they lost vision in both eyes and this was noted by parents and guardians earlier.

One patient presented at 12 years of age with a history of leueocoria for two years. Histology had confimed retinoblastoma with extra-scleral spread. Two hypotheses can be put forward to explain this unusual late presentation. It is possible that there was wrong data entry by the attending clinician on presentation or possibly this patient had a yet-tobe discovered variety retinoblastoma that is indolent and very slowly progressing. Nevertheless, this patient died within one year of presentation to the hospital.

The late presentation was also reflected in the clinical presentation of the disease (Figure 3 and Table 2). Only eight of the 160 (5%) patients included in this study presented with early disease amenable to focal treatment. This presented a down ward trend from a study done previously in the same institution that found 10% of the patients being amenable to focal treatment (2). This apparent down ward trend was also reflected in the ocular examination results that showed 38% having leucocoria, 20% having orbital inflammation while 22% of patients with proptosis. The previous study had found 73.2, 3 and 16% respectively (unpublished). These results compare well to studies done elsewhere in Africa. In Tanzania, study found leucocoria in 56% of patients, proptosis in 30%, lid swelling in 28% and strabismus in11 % (33). In Nigeria, study revealed proptosis with chemosis to be the most common presentation (9).

Histologically, 76.5% of enucleated eyes had histology (Table 4). The rest of the reports may have been misplaced during data storage. Some patients were also referred with no histology reports after enucleation. Only 3.7% of the cases had moderate differentiation, no cases were reported as highly differentiated while the rest all had poorly diffentiated tumours. This correlates with the study done in Uganda which found 96% of cases having poor differentiation (2). In total about 59% of the enucleated eyes had pathologic risk factors for metastasis that is, optic nerve invasion, choroidal invasion and extrascleral spread. These patients would require adjuvant chemotherapy or radiotherapy after the primary enucleation. This compares with a study done in India that reported 54% of 142 eyes having risk factors for metastasis but differs from results of a study done in the USA that found only 18.5% to have high risk for metastasis (11,12). In Uganda, found the risk factors in 60% of 25 eyes while the Tanzanian study found the factors in 45% of 36 eyes (4,10). These study results differs with findings in developed world where patients present earlier than in our set up. It is prudent to apply caution in analysis because of the missing data as mentioned earlier. Unavailability of histology was a challenge that was encountered in this study as well as the study done in Tanzania where only 35% of cases had histology confirmation (4).

The unavailability of histology confirmation of retinoblastoma in our set up is further compounded by long delays of reporting after enucleation. The mean duration was two and a half months (SD 4.2) with a range of three days and four months (Figure 4). This delay has often necessitated use of clinical diagnosis to commence primary and secondary treatment where it was needed. Clinical diagnosis of retinoblastoma, before primary treatment, would largely be accurate as retinoblastoma is the only common tumour that exhibits both intra-ocular and extra-ocular signs. The intra-operative findings at enucleation on the extent of tumour spread has been used to plan secondary

management if there was optic nerve thickeness, retrolaminar spread beyond resection margin or extrascleral spread. This study sought to compare the surgeon's findings with histology report (as the gold standard) where they were available. The sensitivity was found to be 69.4% while the specificity was 69.6%. The accuracy was 69.5% (Table 5).

There were long delays between enucleation and histopathological reporting in this study (Figure 4). More than half (52%) of reporting was done more than two weeks after surgery and this would have resulted in delay in commencement of adjuvant therapy where indicated. In addition, it will be important in the future to format the histopathology reports in accordance to international standards of retinoblastoma reporting (13).

In conclusion, there was late presentation of retinoblastoma cases treated at Kenyatta National Hospital. This is similar to the trend observed in studies done 15 years earlier at the same institution. Histopathological confirmation of retinoblastoma is hampered by missing reports, incomplete information on disease spread and long delay in reporting after surgery. Missing data, inadequate data entry and an incomprehensive referral system are challenges in the management of retinoblastoma in our setting.

ACKOWLEDGEMENTS

To the staff in the medical records department at the Kenyatta National Hospital. Special thanks to the Christoffel Blindenmission (CBM) for financial support.

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