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Retinoblastoma – A 20 year review from the University Hospital Kuala Lumpur

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Summary

Retinoblastoma was clinically diagnosed in 38 patients in the University Hospital between 1968 to 1988. White pupil or cat's eye reflex, found in 25 patients, was the most common symptom. Four patients refused any form of treatment. Of the 27 histopathologically confirmed cases, 16 were males and 11 were females . There was no ethnic group predominance, although a male preponderance was observed among Malay patients (M:F 3:1, $p < 0.05$). Treatment in cases with unilateral disease, without extra ocular extension consisted of enucleation of the involved eye, with close examination of the contralateral eye in follow-up. In cases presenting with bilateral tumour the worse eye was removed. Of 20 cases of histopathologically proven unilateral retinoblastoma treated surgically, 12 patients survived for a mean period of 4.5 years (Range: 1-19 years). The defaulter rate for this group of patients was 55%. None of the 7 cases of bilateral retinoblastoma survived beyond 5 years (Mean survival 2.5 years).

Key words: Retinoblastoma, cat's eye reflex, enucleation, irradiation or cryocoagulation, chemotherapy, traditional man, multidisciplinary cooperation, education of parents.

INTRODUCTION

Retinoblastoma is the most common intraocular malignant tumor occurring in childhood. The overall incidence of retinoblastoma is said to be 1 in 18,000 – 30,000 births.[1] In some cases a dominant gene is transmitted from parent to offspring particularly in cases of bilateral tumors. The tumor may also occur as a sporadic somatic or genetic mutation[2] Recently a retinoblastoma anti-oncogene has been identified at Q14 on the 13th chromosome. If this retinoblastoma blocking gene is absent in both genetic loci, retinoblastoma results.[2] In the United States, between 1960 – 1967, Jensen and Miller reported a marked racial difference in mortality from retinoblastoma with black children experiencing a mortality 2 1/2 times that of white children.[3] However, if the disease is diagnosed early and the appropriate treatment instituted, the 5 year survival rate is 90%[4]

MATERIALS AND METHODS

The cases in this study include all patients seen at the Department of Ophthalmology between 1968 – 1988. In this retrospective study; a total of 38 cases were seen, 27 of which were histopathologically confirmed as retinoblastoma. All patients were analyzed according to age, ethnic groups and sex.

The clinical diagnosis of retinoblastoma was made on fundal examination. C.T. Scan was only available in late 1981, and cases seen after this received routine scanning. The involved eye was removed in unilateral cases and the more severely involved eye was removed in bilateral cases. All specimens were sent for histopathological diagnosis.

Treatment

Bilateral enucleation was not performed as a rule. During surgery, a detailed examination of the uninvolved retina was carried out after full dilatation of the pupil using the indirect ophthalmoscope. Every three months a detailed examination of the eye was done either under general anaesthesia or in the outpatient clinic depending upon the cooperation of the patient, until adulthood was reached.

In children with bilateral involvement, the second eye was treated with irradiation or cryocoagulation depending on the size of the tumor. If the excised end of the optic nerve of the enucleated eye was found to be infiltrated or metastases were present, adjuvant chemotherapy is administered, after the course of irradiation.

RESULTS

Demographic Data

Age, Sex and ethnic group

Table 1 summarizes the distribution of cases by sex and ethnic group in the 27 cases of histopathologically proven retinoblastoma. Of these 27 cases, 23 (85.2%) were between the ages of 1 $^1/_2$ years to 3 1/2 years, at the time of diagnosis. Only 4 patients were less than 1 year old.

Table 1
Distribution of Cases by Sex and Ethnic Groups

Ethnic Group	Malays (No / %)	Chinese (No / %)	Indians (No / %)
Male	7	8	1
Female	2	8	1
Total	**9 (33.3%)**	**16 (59.3%)**	**2 (7.4%)**

16 of the 27 (59.3%) confirmed cases were Chinese followed by 9 Malays (33.3%) and 2 Indians (7.4%). Among the Chinese and Indians, male and female were equally affected whereas in the Malays 77.7% were males and this increased the overall incidence in males to 59.3%. These results were statistically analyzed using the Chi-square test. When compared with hospital admissions over the same 20 year period, there was no significant difference in the occurrence of the disease in various ethnic groups ($p > 0.05$). The male preponderance in Malays, however, is statistically significant ($p < 0.05$).

Laterality and Clinical Features

Cat's eye reflex or white pupil was present in 73.7% of the patients. Other presenting features are shown in Table II.

In 20 (74%) unilateral cases, the right eye was involved in 12 patients (60%). Of the 7 bilateral cases, 5 (71.5%) were males.

Pathology

Of the 34 patients all of whom had one eye enucleated, histopathological examination was at variance with the clinical diagnosis in 7 patients (20.6%).

Table 2
Signs, Symptoms and Other Features in Decending Frequency of Presentation

1.	Pupil fixed and dilated	10.	Pain in the affected eye
2.	Calcified lesion in orbit (X-ray)	11.	Squint
3.	Optic nerve involvement (C.T.Scan)	12.	Cataract
4.	Proptosis	13.	Ciliary staphyloma
5.	Raised intraocular pressure	14.	Iris nodule
6.	Convulsions	15.	Rubeosis
7.	Extraocular fungating mass	16.	Nystagmus
8.	Photophobia	17.	Retinal Detachment
9.	Opaque cornea		

Treatment and Follow-Up
Patients not treated surgically

Of the 38 clinically diagnosed patients, 4 (10.5%) refused surgery and discharged themselves against medical advice and two of them were lost to follow up. One patient agreed to undergo radiotherapy and chemotherapy only (without surgical intervention 6 months after diagnosis). She was last seen 12 months later and was alive. The fourth patient had bilateral retinoblastoma, refused admission, and is currently undergoing 'traditional treatment' elsewhere and is alive 1 year after diagnosis.

Patients treated surgically
Unilateral disease

In this series, of the 20 cases of unilateral retinoblastoma, 12 survived between 1 and 19 years (mean 4.5 years). 3 patients died shortly after diagnosis, between 3 and 8 months. Of the remaining 5 cases, nothing is known as their follow up appointments had not been kept. However, these last 5 patients presented with advanced disease and are unlikely to have survived for more than a year. After the initial treatment was completed, more than half (55%) of the patients were lost to follow up completely.

Bilateral disease

Of the 7 cases of bilateral retinoblastoma, available data shows that 5 survived between 1 and 5 years (mean 2.5 years) and 2 died between 4 months and 2 years after diagnosis.

DISCUSSION

It is sometimes difficult to compare statistics from Western centres with local data on retinoblastoma patients. Some of the local problems relate to late stage of disease at the time of presentation, poor patient compliance and a high defaulter rate.

The results show that the treatment of unilateral retinoblastoma is good. Although there is a 55% defaulter rate after the initial therapy is completed, it is likely that many of the cases were cured, as

data from other studies have shown.[2] Spontaneous regression of retinoblastoma is a well-recognised phenomenon, and it is possible that this may have occurred in some of our cases.

Religious and ethnic taboos often prevent adequate [although from the parent's viewpoint multilating] surgery to be practiced. If enucleation is proposed as part of treatment consent for surgery is often refused. Some parents only agree if therapy is non-surgical. Belief in traditional faith healers is still strong, and such non-medical therapy is often sought after in these cases. Patients who are ultimately brought into hospital are often in advanced stage of the illness, and curative therapy is often impossible (Fig. 1). Poor patient compliance and defaulting follow-up is a serious problem in treated patients. In the Third World context, therefore, we need to formulate a sensible policy to treat these cases – and we advocate saving the child before the eye instead of trying to save both the child and the eye. Recently more patients and parents are receptive to accepting radical surgical therapy. We hope that this trend, together with an improved follow up rate will allow future studies within the next decade to be conducted, where a multicentric statistical evaluation of data would be possible. Ideally, an actuarial survival study would be most informative, individualizing cases according to stage of disease and studying the outcome. At the present time, however, this is not possible.

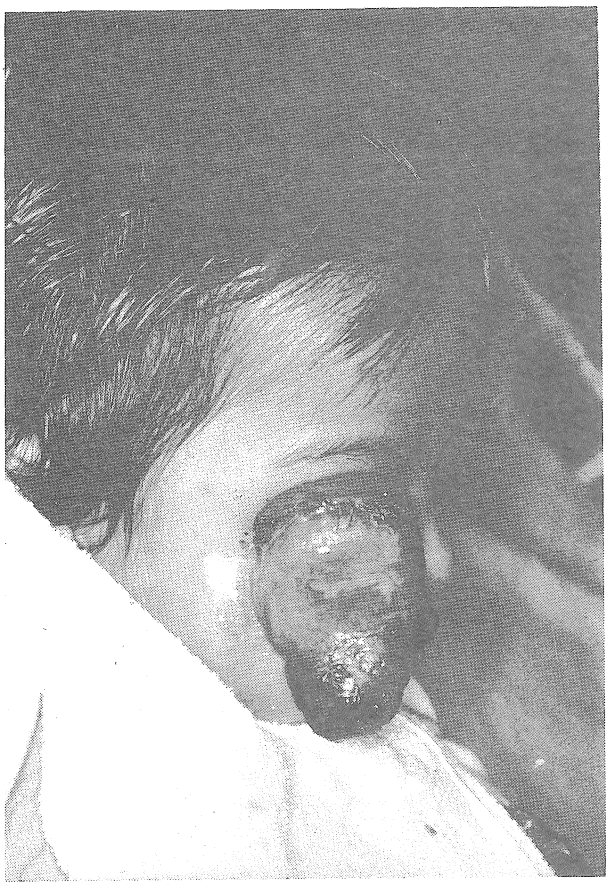

Fig. 1
Right retinoblastoma, presenting as a fungating mass, with extensive local spread

As noted earlier, we do not as a rule perform bilateral enucleations. However, in 1977, one patient had both eyes removed for bilateral retinoblastoma. Another patient required enucleation of both eyes for bilateral retinoblastoma with local extensions, but treatment was refused by the parents.

Studies have shown that 1 in 20 patients develops a tumor in the second eye.[5] One of our patients developed a tumor in the second eye 14 months after enucleation of the first eye. An appropriate artificial eye was fitted in a prosthetic center about 2 months after surgery.

Most of the cases of those who died were first seen either with extra ocular infiltration or distant metastasis. The treatment regime is widely varied, and we as a routine prefer to enucleate all cases of unilateral tumor, if consent is available.

Because of high rate of defaulters in follow up among our patients, we have tended to advocate enucleation more frequently than other centers[5] Periodic follow up would have been required if other forms of treatment such as cryotherapy, light coagulation, focal irradiation, etc. are used.

As most of our patients seek treatment late (average 6 months after first symptom) the signs and symptoms were advanced in many cases. The common presenting signs and symptoms are shown in Table II. In our series, both sexes were equally affected in unilateral cases. Among the 7 cases of bilateral tumors, 5 were males though our cases were small in number and statiscally not significant. On the contrary, in a survey by the National Cancer Institute between 1969-1971, it was found that in unilateral retinoblastoma both sexes were equally affected but among bilateral cases, there was a striking female preponderance[6]

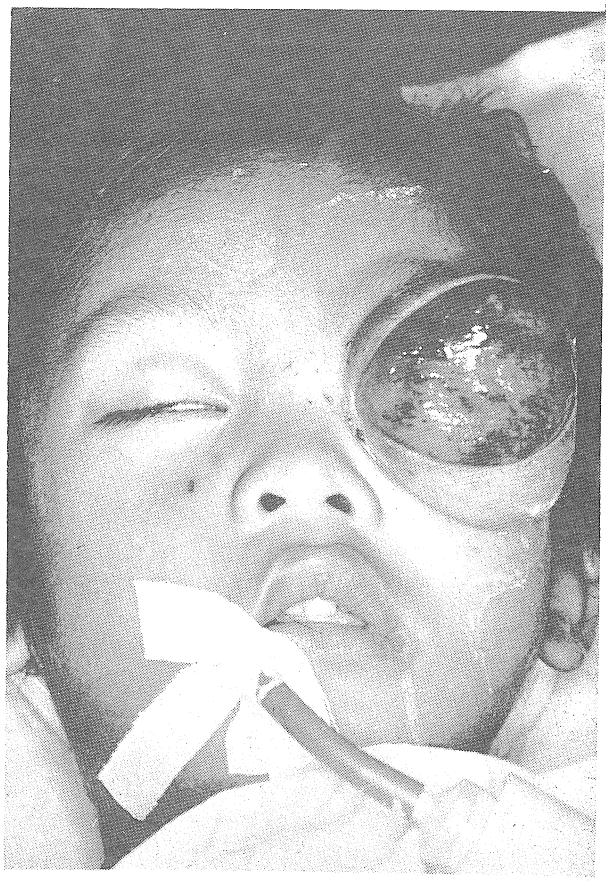

Fig. 2
Extraocular extension of left retinoblastoma

After radiotherapy, there is an increased risk of late development of a second primary usually osteogenic sarcoma in the area of irradiation[5] In our series we have not seen this complication as most of our patients default follow up.

The current trend in the treatment of retinoblastoma is towards a more conservative approach. But this is only possible in hospitals that are specifically well equipped and such an approach has achieved excellent results without any changes in the survival rate[7]

The detection and clinical differentiation of retinoblastoma from simulating lesions may be difficult. In our series as many as 20.6% of the eyes enucleated did not show a tumor as compared with Robertson and Campbell's series where 16% of eyes enucleated with clinical diagnosis of retinoblastoma were found on pathological examination to have lesions other than retinoblastoma[8]

There are many types of treatment available, such as, irradiation of the whole eye with cobalt beam unit, focal irradiation with cobalt plaques, light coagulation, cryosurgery, cytotoxic drugs and enucleation. As a matter of fact, the treatment needs multi-disciplinary cooperation from ophthalmologist, pathologist, oncologist and radiotherapist. A comprehensive fundal examination is very important as emphasized by Ellsworth, who noted that 75% of his patients had tumours situated anterior to the equator.[9]

In the series of Bedford et al the only indication for enucleation was involvement of the optic nerve[10] In my opinion, the management of retinoblastoma in this part of the world should include the following criteria. Parents and patients (where relevant) should be educated on:

(a) the seriousness of the disease
(b) the need to accept recommended treatment and
(c) the importance of periodic review of the status of the disease

CONCLUSION

We hope to educate the parents of patients with clinical diagnosis of retinbolastoma on the seriousness of the disease and the poor prognosis of untreated retinoblastoma. The survival rate in unilateral or bilateral cases is about 92% as reported by Bedford which means to show that retinoblastoma is a type of cancer that can be treated successfully.[2] Early diagnosis and prompt treatment can further increase the survival rate. In this study, the poor survival rates of our patients were due to refusal of surgery, a high defaulter rate (15%), and the tendency to seek a miracle cure from native healers, trends which must be reversed by adequate parent education.

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