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Retinoblastoma in Iraqi Children, the Experience of Children Welfare Teaching Hospital

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Abstract:

Background: Retinoblastoma is the most common intraocular tumor affecting young children.
Objectives: To review the clinical presentation and treatment outcome of retinoblastoma in children treated at the Children Welfare Teaching Hospital, Baghdad.
Patients and Methods: A review of 32 children with retinoblastoma, diagnosed and treated at the Oncology Unit, Children Welfare Teaching Hospital, Medical City, Baghdad from 1999 to 2006.
Results: Among 32 patients, 56.25% were males and 43.75% were females with a median age of 34.5 months. Unilateral disease was observed in 19 patients. Leukocoria was the most common presenting feature. Advanced stages were predominant in half of the patients. Chemotherapy following eye enucleation was the mainstay of treatment. The disease-free survival was 23.33% while the mortality rate was 26.67%.
Conclusions: This single center study reported a poor outcome and a low disease-free survival due to high frequency of advanced stages and abandoning treatment by the parents.
Keywords: Retinoblastoma, children, outcome.

Introduction:

Retinoblastoma (RB) is a relatively rare childhood cancer. It is the most common ocular malignancy in childhood.(1, 2) There are hereditary and non-hereditary forms of the disease and it can be unifocal or multifocal.(3) This cancer is initiated by a genetic mutation in tumor suppressor gene on chromosome 13 called the *RB1* gene. The defective *RB1* gene can be inherited from either parent. Inherited forms of RB are more likely to be bilateral.(4, 5) The tumor is composed mainly of undifferentiated anaplastic cells that arise from the nuclear layers of the retina.(3) The most common presenting sign is leukocoria (white pupil) which is usually noticed by family members and described as a cat's eye appearance. Other cases present with strabismus, squint or features related to metastasis.(2, 6) Early diagnosis and intervention is critical to successful treatment of the RB. The investigations required for establishing the diagnosis and stage include fundoscopic examination, imaging studies, fine needle aspiration and biopsy, cerebrospinal fluid analysis, bone marrow examination, DNA analysis and karyotyping.(7, 8) Untreated RB is almost always fatal. The management of RB involves a multi-specialty team and aims to save the vision and life of the patient.(8, 9) Primary enucleation combined with chemotherapy, radiotherapy, laser photocoagulation or cryotherapy is usually planned.(10) Prognosis depends on many factors like stage of the disease has significantly improved over the last decades.(8)

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Patients and Methods

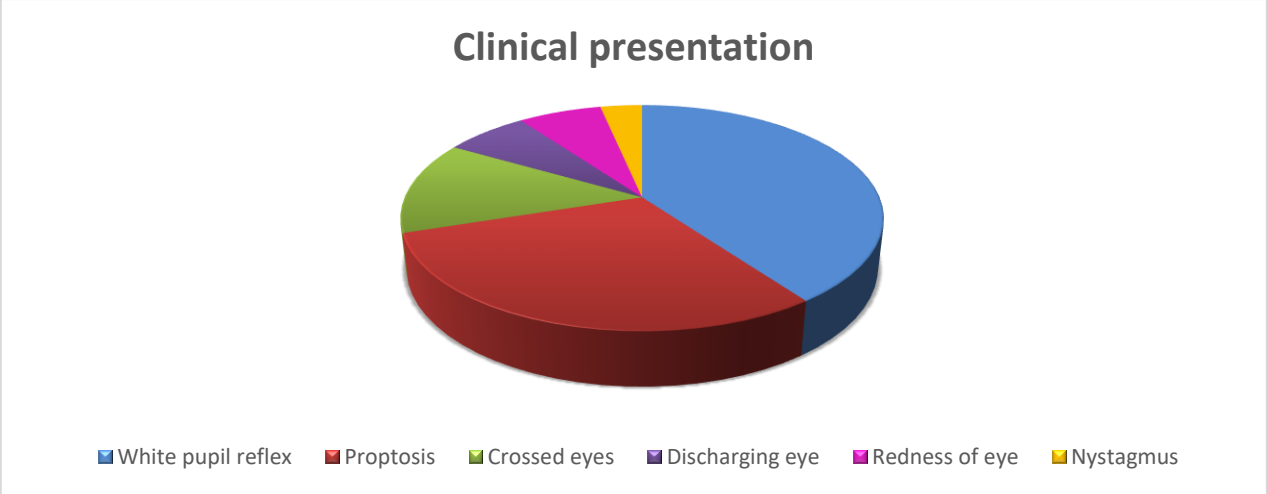
A review study of 32 consecutive pediatric patients with RB diagnosed and treated in the Oncology Unit, Children Welfare Teaching Hospital, Medical City, Baghdad, during the period from January 1999 to December 2006. Information regarding age, gender, clinical presentation, investigations, staging, histopathological typing, treatment modalities, follow-up and outcome were reviewed. The diagnosis was established by either histopathological examination (by different histopathologists) of specimens taken by surgical enucleation or ophthalmological examination.

The disease was staged by Grabowski-Abramson staging system.(11) Patients with retinoblastoma were treated by enucleation, laser photocoagulation and chemotherapy. Evaluation of outcome depends on the WHO criteria for assessing response to treatment in solid tumors.(12) Statistical analysis was done using SPSS software, 2007. Descriptive statistics like frequency, percentage, mean and median values were calculated.

Results:

Among 32 patients diagnosed with retinoblastoma, 18 (56.25%) were males and 14 (43.75%) were females with a male to female ratio of 1.28:1. Ages at diagnosis ranged between 7 - 62 months with a median age of 34.5 months.

Twenty three patients (71.9%) had no family history of retinoblastoma, 2 patients (6.2%) had positive family history (first and second degree relatives) of retinoblastoma, while, seven patients (21.9%) had family history of tumors (at any age) other than retinoblastoma. Patients presented with unilateral retinoblastoma in 19 cases (59.4%) while 13 cases (40.6%) were with bilateral retinoblastoma. The presenting clinical features are shown in figure (1).



* Patients may present with more than one symptom or sign.

Figure (1): Presenting clinical features.

According to Grabowski-Abramson staging system, none of the patients presented in stage I, 14 (43%) presented in stage II, 7 (21.9%) in stage III, 5 (15.6%) in stage IV and 6 patients (18.8%) in stage V.

For the 32 patients, treatment was mainly by eye enucleation followed by chemotherapy using either RB protocol, JOE protocol or a combination of both protocols for 4-6 cycles (13, 14). None of the patients had received radiotherapy except one patient treated with photocoagulation, table (1).

Table (1): Treatment modalities.*

Treatment modalities	No. of patients	Percentage
Enucleation	30 (Done)	93.75
	2 (Refused)	6.25
Chemotherapy	30 (Treated)	93.75
	R.B. protocol 8	
	JOEprotocol 15	
	Both regimens 7	
	2 (Refused)	6.3
Photocoagulation	1 (Treated)	3.3

*One patient received more than one line of treatment.

Depending on the WHO criteria for assessing response to treatment in solid tumors, the outcome is as shown in table (2).

Table (2): Outcome of treatment

Outcome	No. of patients*	Percentage
Disease-free**	7	23.33
Progressive disease	8	26.67
Lost to follow- up	7	23.33
Death	8	26.67
Total	30	100

*Guardians of two patients refused treatment.
**Over period ranging from 18-96 months.

Death was due to central nervous system involvement in 6 out of 8 dead patients (75%) or metastasis to other sites in the other 2 patients (25%).

Statistical analysis:
Statistical analysis was done using SPSS software, 2007. Descriptive statistics like frequency, percentage, mean and median values were calculated.

Discussion:
Regarding age and gender, the results in the present study are to some extent similar to the findings of a Brazilian study in 2004 (15) where 52.3% were males and 47.7% were females with a male to female ratio of 1.1:1 and a lower median age of 22.2 months at presentation than our series (34.5 months) probably due to delay in detection and referral. The current study documented that 6.2% of the patients had a positive family history of retinoblastoma, compared to the results of an American study in 2002 (16) where 14% of the patients had positive family history.
In our series, 40.6 % had a bilateral disease, higher than the findings of an Indian study published in 2002 (17) and an American study in 2016 (18) where 16.3% and 28.9% of the patients, respectively, had bilateral disease. This difference may be due to a more aggressive nature of the disease in our series or because of the delay in the detection and referral resulting in advanced stages at presentation. White pupil reflex (leukocoria) was the most common clinical manifestation at presentation (37.5% of patients), but was still lower than the findings of the Brazilian study (15) where leukocoria was seen in 79% of the patients.
Using Grabowski-Abramson staging system, (11) no patients in our study were reported to be in stage I at presentation, while 34.3% were in stages IV and V, compared to results of an Argentinian study in 1998 (19) in which 64.2% of the patients were in stage I and only 6.3% were in stage IV & V. Extraocular extension of the disease was more common in our patients probably due to delays in seeking medical advice by families and lack of awareness of some ophthalmologists and pediatricians about the importance of early intervention.
In the current study, enucleation followed by chemotherapy was a standard initial treatment modality and was performed in 93.75% of the patients which is much higher than what was reported in an American study in 2002 (16) where only 32% of their series were managed by enucleation due to extraocular extension of the disease and eye damage by the tumor. Local therapy like photocoagulation (laser therapy) was done in only one patient in our series, while none of the patients received external radiotherapy. This is due to the lack of facilities as there is a single radiotherapy institute in Baghdad that has a long waiting list (for many months) and its radiotherapy machines are out of order most of the time. (20) Due to all the mentioned limitations in the diagnosis and treatment, the survival of patients was not promising. At the time of final data entry, 23.3% of our patients were disease-free and 26.7% had already passed away, compared to the findings of an East African study published in 2008 (21) where 36.2% of the patients were disease-free and only 7% had passed away. The low rate of disease-free survival and high death rate in our cases are due to high percentage of patients who have abandoned treatment due to many reasons such as living outside Baghdad or because of the difficult security conditions in the country in that period. Progressive disease and CNS involvement were the main presumptive causes of death, 75% died due to CNS involvement, compared to findings of a Turkish study in 2007 (22) where death due to CNS involvement was reported in only 7.7% of the patients. Our study shows a higher rate of CNS metastasis due to the large number of cases with advanced stages of the disease at presentation and intracranial extension.

Conclusions:
The study reported a poor outcome with a low disease-free survival perhaps due to late presentation with more advanced stages, lack of essential facilities and abandonment of treatment by the guardians. More awareness about retinoblastoma among health workers as well as the public and encouraging a multi-disciplinary team approach at highly specialized centers are vital in diagnosing and managing such a rare cancer.

Author's contribution:
Dr. Salma A. Al-Haddad conceived and planned the experiment. Dr. Mazin F. Al-Jadiry supervised the findings of this work and provided the administrative and technical support. Dr. Rasim M. Al-Jumaily contributed to the collection of data and interpretation of results. Dr. Areej E. Kadhom took the lead in carrying out the statistical analysis. All authors contributed in writing the manuscript and provided critical feedback in final shape of manuscript.

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سرطان شبكية العين عند الاطفال العراقيين، تجربة مستشفى حماية الأطفال التعليمي

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الخلاصة
الخلفية: : سرطان شبكية العين هو ورم العين الأكثر شيوعاً الذي يصيب الاطفال الصغار.
الأهداف: مراجعة الاعراض السريرية واستجابة سرطان شبكية العين عند الأطفال الذين عولجوا في مستشفى حماية الأطفال التعليمي في بغداد.
المرضى والطرق: أجريت دراسة مراجعة على 32 طفل عراقي مصاب بسرطان شبكية العين، تم تشخيصهم وعلاجهم في وحدة الامراض السرطانية في مستشفى حماية الأطفال التعليمي في مدينة الطب في بغداد في الفترة من 1999 الى 2006.
النتائج: من بين 32 مريضا ، كان 56.25 ٪ من المرضى ذكوراً و 43.75 ٪ إناثاً مع متوسط عمر يبلغ 34.5 شهراً. قد لوحظ المرض في جانب واحد في 19 مريضا، وكان الانعكاس الابيض للبؤبؤ أكثر الاعراض السريرية شيوعاً وكانت المراحل المتقدمة للمرض هي السائدة في 33.4% من المرضى. كان العلاج الكيميائي الذي يعقب الاستئصال الجراحي للعين هو الدعامة الأساسية للعلاج. بلغت نسبة البقاء على قيد الحياة خالياً من المرض 23.33٪ في حين كانت نسبة الوفيات 26.67٪ .
الاستنتاجات: أظهرت دراسة المركز الواحد انخفاض نسبة البقاء على قيد الحياة خالياً من المرض بسبب ارتفاع نسبة تشخيص المرض في مراحل متقدمة و والتخلي عن العلاج من قبل الوالدين.
الكلمات الدالة: سرطان شبكية العين، أطفال، حصيلة.