RESEARCH ARTICLE

Clinical pattern of Retinoblastoma in Pakistani population: Review of 403 eyes in 295 patients

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Abstract

Objective: To document clinical pattern of retinoblastoma in Pakistani population.

Methods: This retrospective study, which was conducted at Department of Ophthalmology, Dow University of Health Sciences, Karachi, reviewed clinical records of patients with retinoblastoma from 1997 to 2012. Staging of disease was done by referring to retinal diagrams, RetCam images, and first magnetic resonance imaging. Ophthalmic notes, imaging reports and histopathology reports of enucleated eyes established optic nerve involvement. SPSS 21 was used for statistical analysis.

Results: Clinical records of 295 patients with retinoblastoma in 403 eyes were reviewed, and male to female ratio was 1.3:1. Retinoblastoma was bilateral in 106(35.93%) patients, while 118(40%) patients had hereditary pattern. Mean age at presentation was 35.98+27.63 months, while mean follow-up was 3±2 months. Leucokoria was the most common presenting feature 173(58.64%) followed by proptosis 72(24.41%). Optic nerve involvement was seen on magnetic resonance imaging or histopathology in 81(20.10%) eyes. Distant metastasis was noted in 32(10.85%) patients on first presentation. Chemotherapy with or without adjuvant treatment was given to 238(80.68%) patients. Enucleation and exentration were performed in 164(40.69%) and 12(2.98%) eyes, respectively.

Conclusion: Most common presenting symptom was leucokoria followed by proptosis. Hereditary retinoblastoma was frequently seen in Pakistani children.

Keywords: Retinoblastoma, Mode of presentation of retinoblastoma, Neoplasms in children, Stages of retinoblastoma, retinoblastoma in Pakistan. (JPMA 68: 376; 2018)

Introduction

Retinoblastoma (RB) is the most common primary intraocular malignancy of childhood.[1] Its incidence varies among different regions of the world between 4.1 per million in Europe[2] to 11.8 children per million in USA.[3] Crude incidence of RB in Mumbai, India, and in our neighbourhood ranges between 4.2 and 3.3 per million among males and females, respectively, with higher incidence in Muslims as compared to other ethnicities.[4] It appears to be more common in poor populations of the world.[5] RB is usually diagnosed by clinical examination and with the help of imaging modalities such as B-scan ultrasonography of eye, CT scan and MRI of orbits.[6] Biopsy of lesion is not performed because of risk of local tumour dissemination.[7] Hereditary retinoblastoma has an autosomal dominant pattern of inheritance and a 90% penetrance.[7] Precursors of cones are said to be most likely cell of origin in RB.[7]

Reported annual crude incidence of RB in Karachi is 4.0/100,000 and 2.4/100,000 in children under the age of 5 and 10 years respectively.[8] Late presentation and delayed referrals are important factors for advanced RB that results in increased rate of enucleation and mortality.[9,10] In a small series of patients, metastatic tumour has been described as initial presentation in 25% cases at single ophthalmic centre of Pakistan,[11] which reflects time lag between disease occurrence and presentation at a proper centre.

Since RB is commonly overlooked and under-diagnosed in Pakistan, we organised a collaborative team in 2008 for proper referral and treatment of RB patients with cost-free management. RB group of Karachi (RBGK) consists of ophthalmologists, paediatric oncologists, radiation oncologists and histopathologists directly involved in the management of childhood malignancies. Karachi is known as 'Mini-Pakistan' because of its multi-ethnic population nearing 20 million. The current study was planned to assess the RB pattern in Pakistan.

Materials and Methods

This retrospective chart-review study was conducted at the Department of Ophthalmology, Dow University of

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Health Sciences, Karachi, and comprised patients who had presented at major ophthalmic centres of Karachi from 1997 to 2012.

It studied the clinical charts and records of examination of patients under anaesthesia with a clinical diagnosis of RB. Eyes with pathologies mimicking RB were excluded. Approval was obtained from the institutional review board. Parents signed informed consent forms in all cases except one, where the patient, being an adult, signed his own consent form.

The ages at first presentation and presenting symptoms were acquired from clinical history.

Gender, laterality of involvement and family history were noted. Patients with bilateral involvement, trilateral involvement and/or positive family history were included inhereditary group. The criteria for positive family were history of at least one parent or one sibling with RB. Staging of disease was done by referring to ophthalmologist's notes of examination under anaesthesia along with their documentation on retinal diagrams and features on magnetic resonance imaging (MRI). RetCam photographs were studied whenever available for staging because RetCam was acquired in 2009 at the department based at Civil Hospital Karachi where all examinations under anaesthesia and necessary ophthalmic management were carried out by one of the authors. Whenever possible siblings also underwent ophthalmic examination along with parents. However, we could not perform tests for genetic analysis of parents, as this facility was not available.

Disease staging was done according to Reese-Ellsworth (RE) Classification, International intra-ocular retinoblastoma classification (IIRC) and Clinical tumour, node and metastasis (cTNM) classification.[7,12-16] Optic nerve involvement was established by MRI and/or on histopathology reports of enucleated eyes. Status of distant metastases at first presentation was also documented. Eyes with group 4 and 5 of RE classification; stage D, E of IIRC classification and stages cT3NM and cT4NM of cTNM classification were labelled as advanced disease.

All data of patients, who underwent examinations under anaesthesia and RetCam evaluations, were entered in computers. A detailed printout stating findings, and details of any intervention done during examination, were given to parents. Parents were also provided with digital versatile disc (DVD) containing RetCam images for their records and for ready reference for other members of RB group and other ophthalmologists.

Data was analysed with SPSS 21. Descriptive statistics were analysed for age, gender, laterality, presenting symptoms and hereditary pattern. Staging of RB by various classifications were presented in bar charts. Statistical significance was calculated between age of presentation of unilateral and bilateral retinoblastoma with t-test. $P < 0.05$ was considered statistically significant.

Results

Out of the 295 patients with RB in 403 eyes, 169(57.29%) were male and 126(42.71%) were female. Male-to-female ratio was 1.3:1. Unilateral RB was seen in 187(63.39%) patients while 106(35.93%) had bilateral involvement. Besides, 2(0.68%) children had trilateral involvement with late evidence of pinealoma. Mean age at presentation in all cases either unilateral or bilateral was 35.98±27.63 months with interquartile range (IQR) of 30(range: 1 month to 22 years). Unilateral cases presented at mean age of 39±25 months and bilateral cases presented at mean age of 31± 31 months. One patient with bilateral RB presented at 22 years of age. After excluding this patient, mean age of presentation of bilateral RB patients decreased to 29 ± 22 months. Difference between age of presentation in unilateral and bilateral RB was statistically significant ($p = 0.018$). Patients of trilateral RB presented at mean age of 14± 14 months. Family history was

Table-1: Comparison of mean ages of presentation of Retinoblastoma in different regions of the world.

Region	Mean age of diagnosis of RB	Mean of diagnosis of unilateral cases of RB	Mean age of diagnosis of bilateral cases of RB
Beijing[17]	2.8 years	-----	-----
Brazil[18]	-------	33.8 months	19.15 months
India[19]	23.98 months	------	-----
Turkey[20]	25 months	29 months	16 months
Iran[23]	28.5 months	27.4 months	30 months
Korea[25]	21.2 months	27.4 months	30 months
China[27]	23 months	27 months	15 months
Malaysia[30]	22 months	29 months	14 months
Pakistan (Present Study)	35.92 months	38.97 months	31.10 months

Table-2: Comparison of presenting symptoms in different regions of the worldPresented as percentage (%).

Presenting Symptom	Pakistan (Present Study)	Beijing[17]	Turkey[20]	Taiwan[21]	Iran[23]	Mali[24]	Korea[25]	China[27]	Singapore[28]
Leukocoria	59.6	67.2	82	71.4	64.8	-----	56	73	50.0
Proptosis	24.3	2.1	8	----	------	54.5	1.4	----	----
Squint	5.1	4.4	10	14.3	-----	-----	8.5	12	13.3

positive in 22(7.50%) patients out of which 10(45.45%) patients had unilateral involvement and 12(54.54%) patients had bilateral disease. Therefore, 118(40%) patients had hereditary pattern of presentation that included cases of unilateral RB with positive family history, and all bilateral and trilateral cases.

Most common presenting symptom was leukocoria, as173(58.64%) patients presented with white pupillary reflex that included 104(35.25%) patients with unilateral RB, 68(23.05%) patients with bilateral RB and 1 (0.34%) patient with trilateral RB.

The second most common presenting symptom was proptosis that was seen in 72(24.41%) patients, while 20(6.78%) patients presented with red eye. Only 15(5.08%) patients presented with squint. Decreased vision was presenting symptom in 8(2.71%) children and 3(1.02%) patients presented with bone pain, while 2(0.68%) children presented with orbital pain and 2(0.68%) children were diagnosed incidentally on sibling screening. Besides, 32(10.85%) children had distant metastases at first presentation which included metastasis in cerebrospinal fluid (CSF)/brain in 21(7.12%) patients and bone marrow metastasis in 11(3.73%). Optic nerve involvement was seen on MRI or histopathology in 81(20.10%) eyes.

Besides, 79(19.60%) eyes with no definite data about staging were excluded from assessment of staging. The remaining 324 (80.40%) eyes were therefore staged according to RE, IIRC, and cTNM classification (Figure).

Only 105(35.59%) patients could be followed up while rest of patients were lost to follow-up. Average follow up of patients was

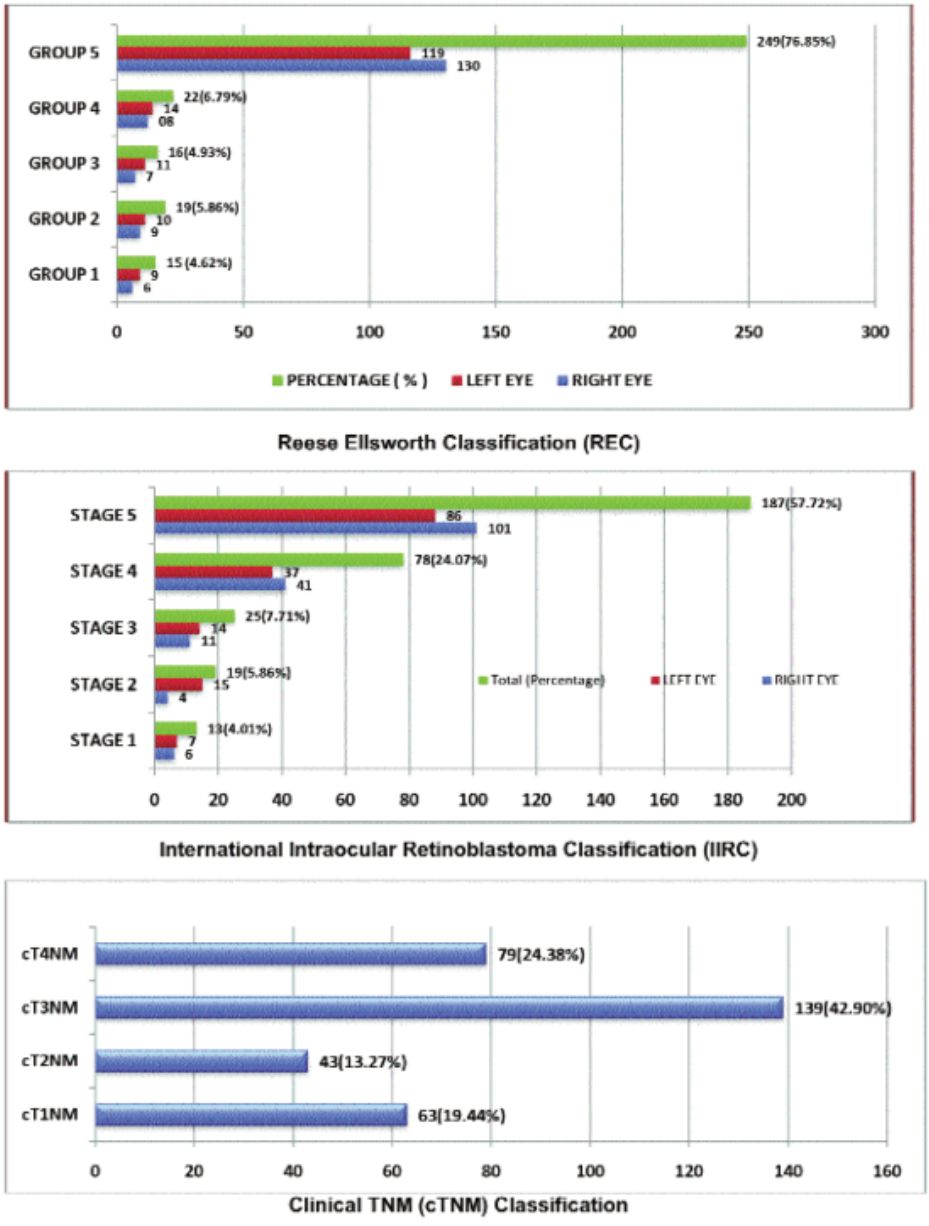

Figure: Staging of 324 eyes out of 403 eyes.

3 months (Range: 1-36 months).

Chemotherapy with or without adjuvant treatment with laser, cryotheraphy, and external beam radiation therapy was given to 238 (80.68%) patients. Enucleation and exentration were performed in 164(40.69%) and 12(2.98%) eyes respectively.

Sixty-seven (22.71%) patients were successfully treated. Parents of 28(9.49%) children refused treatment and left against medical advice while deaths were reported in 10(3.39%) patients. Of successfully treated patients 37(12.54%) patients had recurrence and were treated with further chemotherapy followed by focal lasers or enucleation.

Discussion

Cumulative mean age of presentation in our population was 35.98±27.63 months. This was markedly different from mean ages of presentation in other parts of the world (Table-1). There was trend towards very late presentation in our population. In our population bilateral RB usually presented in age group when unilateral RB presents in other parts of world. Presentations of unilateral RB in our population are even more delayed.[17-23] India is in neighbourhood of Pakistan, and it is not different geographically. Reported age of RB in Indian population is 23.98 months,[19] which is significantly lower than our population.

Present study showed male predominance in ratio of 1.3:1 in our population that is almost equal to what has been reported in RB patients in Mali.[24] Gender distribution varies among different parts of the world, as it is twice more common in males in Korea[25] while in some populations there is no reported gender predominance for RB.[26]

Hereditary RB is fairly common in our population. One hundred and eighteen (40%) patients had hereditary pattern in present study. Same pattern has been reported in Great Britain[27] where 40.8% of patients had hereditary pattern. Other series have reported very few cases of hereditary RB.[24]

Leukocoria was the most common presenting symptom of retinoblastoma in our population. Almost 60% of children of our subset of population presented with leukocoria. Range of presentation of retinoblastoma with leukocoria in different parts of the world varies between 50-82%[17,20-25] (Table-2).

Second most common presenting symptom was proptosis, as 72(24.41%) patients presented with this. Proptosis as presenting symptom is rare in countries with good health facilities and is more common in under-developed countries with poor health facilities.[24]

Eyes with advanced disease are associated with poor prognosis.[22,25,28-30] Reported advanced stage at initial presentation is quite low in European countries.[2] Reported advanced involvement in Asian countries varies from 50% to 80%.[21,24,25,29,30] This trend towards advanced RB seen in Asian countries is similar in this subset of Pakistani population. Apart from proptosis seen in 72(24.41%) patients, distant metastatic lesions were seen on first presentation in 32(10.85%) patients and optic nerve involvement was noted in 81(20.10%) eyes. These findings further augment tendency towards late presentation in our population.

Main reason for late presentations is lack of awareness about RB in general population, poor economic conditions, lack of political commitment on part of government on health affairs and over all poverty. Situation becomes more complex because of poor follow-up and poor compliance on medical advice as is evident in present study. This necessitates need for coordination among national and international bodies to increase awareness among the parents about RB.

In terms of limitations, the current study is retrospective and lacks genetic studies because of its non-availability. RetCam images could not be obtained in all cases as this imaging system was acquired only in 2009 and reliance had to be made on ophthalmic notes and retinal drawings in staging RB. However, this is large study as a result of a collaborative effort of a large group interested in RB and represents pattern of RB in Pakistan.

Conclusion

RB presented as leukocoria in 60%, proptosis in 24% and red eye in 7% children in the study population. Squint as presentation was seen in only 5% patients. RB presented in advanced stage in our population with male predominance. Hereditary pattern was seen in 40% patients. There is need for creating awareness so that tumours may be detected at early stage followed by timely referral. Genetic analysis of parents is also needed for reliable assessment of genetic profile of RB. A collaborative effort with national and international organisations is essential for awareness among parents and for proper management of patients with RB.

Acknowledgements

We are very specially grateful to Dr. Shamvil Ashraf (Pediatric Oncologist) and his team of Children Cancer Hospital Karachi for playing a key role in RBGK, Dr. Uzma Imam of National Institute of Child Health, Prof. Saleh Memon of Al-Ibrahim Eye Hospital, Prof. Javed Niazi and Prof. Alysha Cheema of Jinnah Post Graduate Medical Centre, Dr. Nadeem from Aga Khan University Hospital,

Dr. Syed Fawad Rizvi of Layton Rehmatullah Benevolent Trust Hospital, Dr. Hanif Chatni of Patel Hospital, Dr. Sharif Hashmani and Dr. Misbahul Aziz of Hashmani's Hospitaland all other members of RB Interest Group of Karachi for sharing their data and their help in the management of the patients with RB. We all in RBGK are thankful to all those philanthropists who do not want to be named, who helped and are still helping in the free treatment and management of patients with RB.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

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