

## Retinoblastoma: clinical picture and grouping at the time of first presentation

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### ABSTRACT

**Objectives:** To study the clinical picture and staging of retinoblastoma at the time of first presentation.

**Methodology:** This prospective study of consecutive case series was conducted in the department of ophthalmology, Dow University of Health Sciences and Civil Hospital, Karachi, from October 2007 to September 2009. Twenty patients with unilateral or bilateral retinoblastoma were examined during this period. Parents of every patient were interviewed in detail. Patients were examined under general anesthesia to measure corneal diameter, anterior chamber examination with hand held slit lamp. IOP was recorded with Perkin's tonometer; fundoscopy with indentation was performed with indirect ophthalmoscope. International intraocular classification of retinoblastoma (IICR) was used for grouping of retinoblastoma. Ultrasonography and neuroimaging were performed in all cases.

**Result:** Twenty patients were found to have retinoblastoma with a mean age of 3.86 years (SD=2.56) with a minimum of one year and maximum of 12 years. Out of 20 patients there were 12 (60%) male and 08 (40%) female. Thirteen (65%) were from urban and 07 patients (35%) from rural areas. Family history of retinoblastoma was positive in two patients (10%). Bilateral retinoblastoma was present in 10 patients (50%) and unilateral retinoblastoma in other 10 patients (50%). The most common clinical presentation of retinoblastoma was Leukocoria that was seen in 12 patients (60%) followed by anterior segment involvement in three patients (15%), orbital Cellulitis in three patients (15%), strabismus in one patient (5%) and phthisis bulbi in one patient (5%). Among 10 patients with unilateral retinoblastoma 60% had group E, 20% had group D and another 20% with group C of IICR at the time of presentation. Twenty eyes of 10 patients with bilateral retinoblastoma showed group E in 13 eyes (65%), group D in four eyes (20%), group C in two eyes (10%) and group A in one eye (5%).

**Conclusion:** Leukocoria is the commonest clinical presentation of retinoblastoma. In developed countries 95% of children with retinoblastoma present with limited stage disease and are cured while in our set-up most patients still present with advanced diseases and cure rates are very low. Educational programs are required to educate general public, parents of retinoblastoma patients. Collaboration with pediatricians to check red reflex on every well baby visit is mandatory for early diagnosis.

**KEY WORDS:** Retinoblastoma, Clinical Picture, Grouping.

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### INTRODUCTION

Retinoblastoma is rare but the most common ocular malignancy of childhood, was first described as a specific entity by James Wardrop in 1809, with enucleation as his suggested treatment.<sup>1,2</sup> The incidence of retinoblastoma has been described

1 in 14000 to 1 in 20000 live births depending on the country.<sup>3</sup> About two thirds of patients have unilateral disease and the remaining patients have bilateral disease. Bilateral cases invariably represent germinal mutations. The overall mean age at the diagnosis is 18 months. For unilateral cases it is 24 months and for bilateral cases, 12 months. However, it can present at birth or have its onset in the teenage years or adulthood.<sup>4,5</sup> Diagnosis is made by fundoscopy. Ultrasound, magnetic resonance imaging (MRI) and computed tomography (CT) scans may contribute to diagnosis. Clinically retinoblastoma begins as a small, transparent lesion in the sensory retina. As the tumor enlarges, it becomes white and develops a dilated retinal feeding artery and draining vein and a secondary retinal detachment can occur. The most frequent presenting sign of retinoblastoma is Leukocoria, a white pupillary reflex. As the tumor enlarges it can leave its intraretinal location and assume an exophytic, endophytic growth pattern or a combination of two. The less common diffuse pattern is characterized by flat growth of tumor.<sup>6</sup> Other clinical presentations include strabismus (crossed or deviating eyes), decreased vision (particularly in bilateral cases), red glaucomatous eyes, retinal detachment, orbital Cellulitis, rubeosis Iridis, pseudo hypopyon (tumor cells anterior to the iris), hyphema<sup>3</sup> or ocular pain.<sup>7</sup>

In developed countries 95% of children with retinoblastoma present with limited-stage disease and are cured; however, in countries with limited resources, like Pakistan, most patients present with advanced disease and cure rates are very low.<sup>8</sup> Early diagnosis is necessary to improve the survival of children with retinoblastoma in these countries. In this article we have highlighted the clinical presentation and staging of retinoblastoma at the time of presentation.

## METHODOLOGY

This study of consecutive cases series was conducted in pediatric eye section of the department of ophthalmology Dow University of Health Sciences and Civil hospital Karachi from October 2007 to September 2009. Parents of every patient with suspected retinoblastoma were interviewed in detail about age of onset, presenting complaints, family history of eye diseases or history of enucleation in family and history of consanguinity was inquired from parents. The ophthalmologic examination was performed under general anesthesia including anterior segment examination with hand held slit

lamp, applanation tonometry with Perkins tonometer and indirect ophthalmoscopy with indentation. The systemic workup was done by a physician and it included physical exam, renal and liver function tests. Cerebrospinal fluid samples bone marrow biopsy were obtained in bilateral retinoblastoma cases. Ultrasonography and Magnetic Resonance Imaging (MRI) was performed in all cases. We used International Intraocular Classification of Retinoblastoma<sup>9</sup> (IICR) (Table-I) for grouping of retinoblastoma. Chemotherapy was given by pediatric oncologist at Children Cancer Hospital Karachi and the patients were referred back to us for eye examination to monitor the response of tumor to chemotherapy. We enucleated all eyes classified as Group E and unilateral group D under the international classification of retinoblastoma. Chemotherapy and tumor consolidation was performed in group C and bilateral group D of IICR.

After treatment, monthly follow-up visits were conducted to examine for residual or new tumors recurrence, and vitreous or sub-retinal seed reactivation. In positive cases, the patient was scheduled for radiotherapy or enucleation. Enucleated eyes were fixed in formaldehyde and studied both macroscopically and under optical microscopy by histopathologist. The pathological examination of the enucleated eyes was conducted with special care to identify the involvement of lamina cribrosa, optic nerve, choroidal invasion, Scleral involvement, tumor necrosis and extrascleral extension. Statistical analysis was done on SPSS version 11 for Windows. In terms of quantitative variables, the analysis included observed minimum and maximum values, calculated mean and standard deviation. For the qualitative variables, the absolute and relative frequencies were calculated.

## RESULTS

From October 2007 to September 2009 twenty patients were found having retinoblastoma with a mean age of 3.86 years (SD=2.56) with a minimum of one year and maximum of 12 years. Of the 20 patients included 10 with unilateral (50%) and 10 (50%) with bilateral retinoblastoma. There were 12 (60%) males and 08 (40%) females. A positive family history of retinoblastoma was present in two cases (10%), 07 patients (35%) were from rural areas of Sind and 13 (65%) were from urban areas.

Most common presentation (Table-II) was Leukocoria found in 12 (60%) followed by orbital Cellulitis in 03 (15%), anterior segment involvement in 03 (15%) squint in 01 (5%) and phthisis bulbi in

Table-I: International Intraocular Classification of Retinoblastoma.<sup>9</sup>

Group	Quick Reference	Specific features
A	Small Tumor	Rb $\leq$ 3mm*
B	Large Tumor	Rb > 3mm* or
	Macular Rb	Located $\leq$ 3mm to foveala
	Juxtapapillary Rb	Located $\leq$ 1.5mm to disc
	Subretinal fluid	Rb with subretinal fluid
C	Focal seeds	Rb with
		Subretinal seeds $\leq$ 3mm from Rb and/or
		Vitreous seeds $\leq$ 3mm from Rb
D	Diffuse seeds	Rb with
		Subretinal seeds > 3mm from Rb and/or
		Vitreous seeds > 3mm from Rb
E	Extensive Rb	Nearly filling the globe or
		Neovascular glaucoma
		Intraocular hemorrhage
		Invasion into optic nerve, choroids, sclera, orbit, anterior chamber

\* Refers to 3mm in basal dimension or thickness.

01 (5%) patient. Of the 10 unilateral cases (Table-III), 06 (60%) presented with group E, 02 (20.0%) with group D and remaining 02 cases (20.0%) with group C of international intraocular classification of retinoblastoma. Of the twenty eyes of ten patients with bilateral retinoblastoma (Table-IV) 13 eyes (65%) presented with group E of IICR, 04 eyes (20%) with group D, 02 eyes (10%) with group C and 01 eye (05%) with group A.

## DISCUSSION

Retinoblastoma is the most common intraocular malignant tumor encountered in children and it



Fig.1: A Survivor of unilateral retinoblastoma. Her daughter had bilateral retinoblastoma.

Table-II: Clinical presentation of Retinoblastoma in 20 patients.

Clinical Presentation	No of Patients	Percent
Leukocoria	12	60%
Anterior Segment Involvement	03	15%
Orbital Cellulitis	03	15%
Squint	01	05%
Phthisis Bulbi	01	05%
Total	20	100%

represents 4% of all pediatric malignancies.<sup>9</sup> In early presenting cases, retinoblastoma remains confined to eye. However, in advanced cases retinoblastoma can secondarily invade the orbit and metastasize to the central nervous system and other distant organs.<sup>10</sup> Untreated retinoblastoma is nearly always fatal.<sup>3</sup> Therefore early diagnosis and treatment is critical in saving lives and preserving visual function of the affected eyes. Extra ocular retinoblastoma is still a problem in many parts of the world and the principal reason for extra ocular spread of retinoblastoma is delay in presentation and diagnosis.<sup>3</sup>

There are three major reasons of death in children with retinoblastoma: CNS and distant metastasis, second cancers and trilateral retinoblastoma. Metastasis affects approximately 5% of patients with retinoblastoma.<sup>3</sup> Metastasis from retinoblastoma occurs most commonly to the CNS, bone and regional lymph nodes. Risk factors for metastasis include retinoblastoma invasion into the uvea, optic nerve and orbit. Neovascular glaucoma increases the risk of orbital invasion of retinoblastoma through the sclera.<sup>3</sup>

It is estimated that in the United States there are approximately 350 newly diagnosed cases of



Fig.2: A three year old child with bilateral extensive retinoblastoma. Her mother was survivor of unilateral retinoblastoma.

Table-III: Grouping of tumor in 10 eyes of 10 pts with unilateral Retinoblastoma.

Group	Frequency	Percent
Group E	06	60%
Group D	02	20%
Group C	02	20%
Group B	00	00%
Group A	00	00%

retinoblastoma yearly, and worldwide estimates are 5000 to 8000 cases each year.<sup>9</sup> India and China estimate 1000 new cases of retinoblastoma each year. In the US and other developed nations 95% of children with retinoblastoma survive their malignancy, where as approximately 50% survive worldwide.<sup>9</sup> The reason for poor survival rates in undeveloped nations relates to late detection of advanced retinoblastoma and the patients usually present with orbital invasion or metastatic disease.<sup>9</sup> In our study 80% of unilateral and 85% of bilateral retinoblastoma patients presented in advanced stages of tumor.

Nearly 50% retinoblastoma cases are heritable due to mutation in the RB 1 gene, which predisposes a child to develop retinal tumors. The hallmark of the majority of hereditary cases is the occurrence of bilateral or multifocal tumors, but 15% of children with unilateral tumors also have a mutation of one allele of the RB 1 gene in their germ cells, that will be inherited by one half of their children.<sup>10</sup> In our study the mother of a child with bilateral retinoblastoma was survivor of unilateral retinoblastoma, managed by right eye enucleation (Fig.1) and her 3 years old daughter presented to us with group E retinoblastoma in both eyes (Fig.2).

If this mother had been informed about the chances of transmitting retinoblastoma to her daughter then she could have brought her for screening or presented her daughter at earlier stage of retinoblastoma and her eyes could have been saved. Fifteen percent of unilateral retinoblastoma patients and all bilateral retinoblastoma patients have a germinal mutation of the RB gene. RB gene mutations are somatic in 60% and germinal in 40% of patients. Over all about 6% of newly diagnosed patients have a family history of the disease.<sup>3</sup> In our study 10% had history of retinoblastoma in family.

The best known clinical sign is leukocoria.<sup>11-13</sup> The next most common presenting sign is strabismus.<sup>14</sup> Retinoblastoma can produce secondary glaucoma in about 17% of cases due to iris neovascularization and secondary angle closure.<sup>15</sup> Inflammation from necrotic intraocular retinoblastoma causes

Table-IV: Grouping of tumor in 20 eyes of 10 pts with bilateral Retinoblastoma.

Grouping	Frequency	Percent
Group E	13	65%
Group D	04	20%
Group C	02	10%
Group B	00	0.00%
Group A	01	5%
Total eyes	20	100%

orbital cellulitis.<sup>16,17</sup> In our study the commonest clinical presentation was Leukocoria seen in 60% followed by orbital Cellulitis 15%, anterior segment involvement 15%, squint 5% and phthisis bulbi 5%.

In this study 65% of bilateral cases and 60% unilateral cases presented with group E. 20% of unilateral and bilateral retinoblastoma cases were having group D, 10% of bilateral and 20 % of unilateral cases presented with group C and 5% of bilateral cases had group A of IIRC. Overall 85% of bilateral and 80% of unilateral cases had advanced retinoblastoma at the time of first presentation. The reason for poor survival in undeveloped nations relates to late detection of advanced retinoblastoma, often presenting with orbital invasion or metastatic disease.<sup>18</sup>

The management of retinoblastoma has gradually evolved over the past years from enucleation to radiotherapy to current techniques of chemotherapy.<sup>18</sup> Eyes with massive retinoblastoma filling the globe are still managed with enucleation, where as those with small, medium or even large tumors can be managed with chemo reduction followed by tumor consolidation with thermotherapy or cryotherapy and visual acuity can be saved particularly in those eyes with extra macular tumors presented at earlier stages.

This study showed that 80% of patients presented in advanced stages that is group D and E of IIRC. An effective screening program is required for awareness and to have patient presented at early stages of disease. This is a sensitive issue which needs extra attention of pediatricians and ophthalmologists to screen children and to detect retinoblastoma at early stages. We need to educate parents and general public about age of presentation and clinical signs to consult eye doctor as soon as possible. Collaboration with general pediatricians who should check red reflex on every well baby visit, orientation of general practitioners who see these patients at first in urban and rural areas for counseling with the parents regarding consequences of disease if not treated at early stages

and for referral at proper time to save their eyes and life.

**Recommendation:** It is recommended that the offspring or a sibling of a patient with hereditary retinoblastoma (germinal mutation) should be examined every 2 to 4 weeks from birth to 3 months, than bimonthly till one year, every 3 months in second year, 4 months in third year and 6 months in fourth year of life. Then yearly office examinations are recommended.

It is also recommended that the offspring or a sibling of a patient with non hereditary retinoblastoma (somatic mutation) should be followed every 3 months during the first two years of age and at 6 months intervals during the next 2 years. Red reflex test should be done by all general pediatricians on every well baby visit. First fundus examination of a normal child should be performed at 6 months of age by an ophthalmologist.

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