Prevalence of refractive errors in children with retinoblastoma

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Victor M Villegas^{1,2}
Shuo-Chieh Wu¹
Timothy G Murray²
Kara M Cavuoto¹
Hilda Capo¹
Craig A McKeown¹

¹Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, FL, USA; ²Miami Ocular Oncology and Retina, Miami, FL, USA

Purpose: The main purpose of this study was to investigate refractive errors in children with unilateral and bilateral retinoblastoma (RB).

Methods: An institutional review board–approved consecutive retrospective cohort study was undertaken. Subjects underwent examination under general anesthesia as part of their RB follow-up, which included evaluation by a single pediatric ophthalmologist. Cycloplegic retinoscopy was performed and keratometry data assessed with a handheld Retinomax K Plus 3 keratorefractometer (Righton Ophthalmic Instruments).

Results: The study included 61 eyes of 37 subjects, with 18 (49%) males and 19 females. Seventeen eyes (28%) had hyperopia with spherical equivalent ≥ 3 D. Refractive astigmatism ≥ 1.5 D was present in 32% of all eyes. Nine (38%) subjects had anisometropia ≥ 2 D. Fifteen (63%) subjects had anisometropia ≥ 1 D.

Conclusion: This study reports the high proportion of amblyogenic refractive risk factors in children with RB, both in RB-affected eyes and contralateral normal eyes.

Keywords: retinoblastoma, hyperopia, myopia, astigmatism, amblyopia, anisometropia

Introduction

Retinoblastoma (RB) continues to represent the most common primary intraocular malignancy in children.¹ Two-thirds of cases are nonheritable (nonfamilial), with normal life expectancy after therapy.² However, a third of cases are heritable due to a germ-line mutation in the *RB* gene.² Newer chemotherapeutic strategies have allowed survival rates that approach 99% in developed countries.³ Globe-salvage rates and visual outcomes have also improved, especially since the introduction of selective intra-arterial chemotherapy and intravitreal chemotherapy, with overall primary salvage rates exceeding 70%.^{4,5}

Refractive errors, including anisometropia and hyperopia, are independent risk factors for amblyopia in children.⁶ A recent study with 3- to 5-year-old subjects ($n=3,869$) established that unilateral amblyopia is present in 12.9% of subjects with hyperopia (≥ 3 – <4 D) and 33.1% with anisometropia (≥ 1 – <2 D), whereas amblyopia alone is present in 4.4% and 3.6% of subjects without hyperopia or anisometropia, respectively.⁶ However, refractive errors in children with RB have not been studied. The main purpose of this study was to investigate refractive errors in children with a history of RB.

Methods

An institutional review board–approved (Larkin Community Hospital-3-012015) retrospective cohort study was undertaken confidentially and according to the tenets

Correspondence: Victor M Villegas
Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, 900 NW 17th Street, Miami, FL 33136, USA
Email v.villegas@med.miami.edu

of the Declaration of Helsinki. Consent to review the medical records was waived by the board, due to less than minimal risk. A chart review of all children with a history of RB that had been evaluated under general anesthesia between 2014 and 2015 was conducted. All subjects were treated primarily with intra-arterial chemotherapy and 810 nm diode-laser ablation. Cryotherapy and radiation were not performed in any subject. Subjects underwent routine examination under anesthesia with cycloplegic retinoscopy and keratometry readings performed by a single pediatric ophthalmologist (VMV). Cycloplegic retinoscopy was performed after instillation of topical proparacaine (0.5%), cyclopentolate (1%), and tropicamide (0.5%). Keratometry data were assessed with a handheld Retinomax K Plus 3 keratorefractometer (Righton Ophthalmic Instruments). Data gathered included age at diagnosis, age at refraction, sex, tumor location, primary treatment, spherical equivalent (SE; sphere + $[0.5 \times \text{cylinder}]$), plus refractive cylinder axis, flat keratometry (K_1), steep keratometry (K_2), and steepest corneal axis.

Results

The study included 61 eyes of 37 subjects, with 18 (49%) males and 19 females. Thirteen subjects had either a phthisic eye or an enucleated socket. Bilateral RB was present in 16 (24%) subjects, with a mean age at diagnosis of 12.0 months. Unilateral RB was present in 21 (76%) subjects, with a mean age at diagnosis of 23.2 months. Age at diagnosis and cycloplegic refraction ranged from 1 month to 72 months. Nine (38%) subjects had anisometropia ≥ 2 D. Fifteen (63%) subjects had anisometropia ≥ 1 D. Tables 1 and 2 summarize the study cohort and refractive characteristics.

When all eyes had been analyzed, 17 eyes (28%) had hyperopia with SE ≥ 3 D. Only two eyes from different subjects had myopia > 2 D. Refractive astigmatism ≥ 1.5 D was present in 32% of all subject eyes. Mean SE was 2.7 ± 4.3 D. Mean refractive cylinder was 1.2 ± 0.9 D. Mean plus refractive cylinder axis was $100.1^\circ \pm 46.2^\circ$. Mean K_1 was 42.8 ± 4.6 D.

Table 1 Characteristics of the cohort (n=37)

	Total (n=37)	Unilateral RB (n=21)	Bilateral RB (n=16)
Male	18 (49%)	9 (43%)	9 (56%)
Female	19 (51%)	12 (57%)	7 (44%)
Enucleation/phthisis	13 (35%)	5 (24%)	8 (50%)
Mean age at diagnosis (months)	18.4	23.2	12
Anisometropia ≥ 1 D	15 (63%)	10 (63%)	5 (63%)
Anisometropia ≥ 2 D	9 (38%)	5 (31%)	4 (50%)

Abbreviation: RB, retinoblastoma.

Mean K_2 was 45.3 ± 2.1 D. Mean steepest corneal axis was $91.9^\circ \pm 34.0^\circ$.

Analysis of the involved eye from subjects with unilateral RB (n=16) was then performed. Twelve eyes (75%) had hyperopia with SE ≥ 3 D. One eye had myopia ≥ 2 D. Refractive astigmatism ≥ 1.5 D was present in 63% of the eyes. Mean SE was 6.9 ± 5.7 D. Mean refractive astigmatism was 1.3 ± 1.2 D. Mean plus refractive cylinder axis was $90.63^\circ \pm 45.3^\circ$. Mean K_1 was 42.0 ± 5.7 D. Mean K_2 was 49.6 ± 1.8 D. Mean steepest corneal axis was $74.9^\circ \pm 30.3^\circ$.

Analysis of the involved eye from subjects with bilateral RB (n=24) was then performed. Three eyes (13%) had hyperopia with SE ≥ 3 D. One eye had myopia ≥ 2 D. Refractive astigmatism ≥ 1.5 D was present in 21% of the eyes. Mean SE was 1.2 ± 1.6 D. Mean refractive astigmatism was 1.1 ± 0.9 D. Mean plus refractive cylinder axis was $99.0^\circ \pm 41.6^\circ$. Mean K_1 was 43.0 ± 2.0 D. Mean K_2 was 44.7 ± 2.6 D. Mean steepest corneal axis was $103.6^\circ \pm 43.2^\circ$.

Analysis of the uninvolved contralateral eye from subjects with unilateral RB (n=21) was then performed. Two eyes (10%) had hyperopia with SE ≥ 3 D. No eyes had myopia ≥ 2 D. Refractive astigmatism ≥ 1.5 D was present in 24% of the eyes. Mean SE was 1.2 ± 1.1 D. Mean refractive astigmatism was 1.1 ± 0.9 D. Mean plus refractive cylinder axis was $108.3^\circ \pm 57.5^\circ$. Mean K_1 was 43.2 ± 1.8 D. Mean K_2 was 45.1 ± 2.2 D. Mean steepest corneal axis was $91.5^\circ \pm 32.6^\circ$. Stratification of SE of all subject eyes by age-group at time of refraction was performed (Table 3). All three groups had similar prevalence of myopia, ranging from 4% to 6%. The prevalence of hyperopia ≥ 2 D decreased with age.

Analysis of RB eyes based on tumor location was then performed (Table 4). Eyes with macular RB had $> 30\%$ more hyperopia and refractive astigmatism compared to extramacular tumors.

Discussion

Management of patients with RB requires a multidisciplinary approach with a pediatric oncologist, ocular oncologist, and pediatric ophthalmologist. Significant improvements in globe-salvage prediction have been made during the last 5 years.^{5,7-10} However, data regarding refractive errors and amblyopic risk factors in children with RB continue to be scarce.

Large studies have validated strabismus and refractive errors being significant risk factors for unilateral amblyopia.^{6,11,12} Mild refractive astigmatism (1–2 D) has been associated with amblyopia in preschool children.⁶ The Multi-ethnic Pediatric Eye Disease Study evaluated over

Table 2 Refractive profiles of all eyes (n=61)

	Unilateral RB eye (n=16)	Bilateral RB eye (n=24)	Contralateral unaffected eye, unilateral RB (n=21)
Hyperopia with SE ≥ 3 D	12 (75%)	3 (13%)	2 (10%)
Myopia ≥ 2 D	1 (6%)	1 (4%)	0
Refractive astigmatism ≥ 1.5 D	10 (63%)	5 (21%)	5 (24%)
Mean SE (D)	6.9 $\pm$ 5.7	1.2 $\pm$ 1.6	1.2 $\pm$ 1.1
Mean refractive astigmatism (D)	1.3 $\pm$ 1.2	1.1 $\pm$ 0.9	1.1 $\pm$ 0.9
Mean plus refractive cylinder axis ($^{\circ}$)	90.6 $\pm$ 45.3	99.0 $\pm$ 41.6	108.3 $\pm$ 57.5
Mean corneal K ₁ (D)	42.0 $\pm$ 5.7	43.0 $\pm$ 2.0	43.2 $\pm$ 1.8
Mean corneal K ₂ (D)	49.6 $\pm$ 1.8	44.7 $\pm$ 2.6	45.1 $\pm$ 2.2
Steepest corneal axis ($^{\circ}$)	74.9 $\pm$ 30.3	103.6 $\pm$ 43.2	91.5 $\pm$ 32.6

Abbreviations: RB, retinoblastoma; SE, spherical equivalent.

6,000 children, and found refractive error to be the most common risk factor leading to amblyopia.¹¹ Anisometropia, refractive astigmatism, and amblyopia seem to affect Hispanic children at a higher rate than other ethnic groups.^{6,11} The Vision in Preschoolers study group determined the prevalence of refractive astigmatism (≥ 1 D) in 3,869 children to be 28.9%. Hispanic patients had the highest prevalence of astigmatism >3.5 D (11.1%) among all ethnic groups studied.¹³ In our study, the most common refractive error risk was refractive astigmatism. Astigmatism ≥ 1.5 D was present in 32% of all eyes, and analysis of refractive astigmatism in eyes without RB showed 24% of eyes had astigmatism ≥ 1.5 D. The study prevalence of astigmatism contrasts with previous historical controls.^{6,13} Hyperopia >2 D has also been associated with amblyopia development in preschool children.⁶ Hyperopia seems to be associated with amblyopia in a dose-dependent fashion.^{6,11,12} In our study, hyperopia >3 D was present in 28% of eyes. Eyes without RB had a low prevalence (10%) of hyperopia >3 D compared to eyes with RB. Eyes with macular RB had the highest mean SE and refractive astigmatism. Prevalence of hyperopia

(35%–55%) and myopia (4%–6%) also seem to be higher in RB patients (1–72 months old) than a previous study, which reported the prevalence of hyperopia and myopia to be 25.56% and 1.20% in 1,507 non-Hispanic children aged 6–72 months old (Table 3).¹⁴ Neuroimaging studies have also shown that eyes with RB have shorter axes, which correlates inversely with tumor volume.¹⁵ The high prevalence of hyperopia in patients with RB may also be partially explained by the hyperopic shift associated with posterior-pole tumor involvement.

Significant anisometropia (≥ 0.5 D) has been associated with refractive amblyopia in $>90\%$ of children.⁶ Hyperopic anisometropia seems to have the lowest threshold for causing unilateral amblyopia. In our study, 15 subjects (63%) had anisometropia ≥ 1 D, and nine subjects (38%) had anisometropia ≥ 2 D.

A recent study performed in Taiwan found with-the-rule astigmatism to be the most common.¹⁶ The cyclorefractive cylinder axis was similar to the corneal cylinder axis.¹⁶ Correspondingly, with-the-rule astigmatism was the most common in our study, including nontumor eyes.

Visual acuity potential in eyes with RB is not well understood. Historically, eyes with RB had a guarded prognosis. Recent studies have demonstrated improved visual outcomes.^{17–23} A study that evaluated visual outcomes in 12 children with macular RB found that 80% of eyes with

Table 3 Prevalence of hyperopia and myopia in all subject eyes stratified by age at cycloplegic refraction

	1–11 months (n=20)	12–23 months (n=17)	24–72 months (n=24)
Hyperopia (SE $\geq +2.0$ D)	11 (55%)	6 (35%)	6 (25%)
Myopia (SE ≤ -1.0 D)	1 (5%)	1 (6%)	1 (4%)
Mean SE	3.1	2.4	2.7
SD	3.7	3.4	5.4
Standard error	0.8	0.8	1.2

Abbreviation: SE, spherical equivalent.

Table 4 Mean refractive error and RB location

	Mean spherical equivalent (D)	Mean refractive astigmatism (D)
Macular RB (n=28)	3.7 $\pm$ 5.0	1.5 $\pm$ 1.0
Extramacular RB (n=12)	2.6 $\pm$ 5.3	1.0 $\pm$ 0.67

Abbreviation: RB, retinoblastoma.

macular involvement had improvement of visual acuity following occlusion therapy.²¹ This suggests that subjects with macular RB have diminished vision beyond the level expected for the burden of ocular pathology. Our study found a significant prevalence of high refractive errors in children with RB that may lead to amblyopia.

Limitations of our study include its retrospective nature and sample size. Because RB is a rare disease, extensive studies are likely to be limited. Chemotherapy, number of laser treatments, tumor size, tumor-growth pattern, visual acuity, cataracts, and clinical changes were not evaluated. Further studies may elucidate if any correlation with refractive errors exists.

This study reports the high proportion of children with RB that have amblyogenic refractive risk factors in both RB-affected eyes and normal contralateral eyes in unilateral cases. It is likely that significant expertise in pediatric refraction and amblyopia treatment may help these children achieve maximal visual potential. Further studies are needed to evaluate the prevalence of amblyopia in children with RB.

Ethical approval

An institutional review board–approved (Larkin Community Hospital-3-012015) retrospective cohort study was undertaken confidentially and according to the tenets of the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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