Retinoblastoma in younger versus older children: Clinical features and outcome

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Précis:

Over a mean follow-up period of 41 months in younger children (age <5 years) and 42 months in older children (age >5-20 years) with retinoblastoma, younger children had better chances of globe and life salvage.

Abstract

Purpose: To compare the clinical presentation and outcome of younger (age less than 5 years) and older (aged 5 to 20 years) Asian Indian children with retinoblastoma (RB)

Design: Retrospective comparative study

Subjects: 1940 eyes of 1350 children aged <5 years (group 1) and 123 eyes of 100 children aged >5-20 years (group 2).

Intervention: Transpupillary thermotherapy, Cryotherapy, Systemic chemotherapy, Enucleation

Main outcome measures: Globe salvage, systemic metastasis, and death

Results: The mean age at diagnosis of retinoblastoma in group 1 was 24 months (median, 23 months; range, <1 to 60 months) and in group 2 was 84 months (median, 79 months; range, 61 to 210 months). There was no gender predilection in either of the groups. Bilateral involvement was more common in group 1 compared to group 2 (44% vs 22%; p=0.0001). On comparison of group 1 versus group 2, leukocoria (77% vs 54%; p=0.0001) was the more common presenting complaint in group 1, while proptosis/enlarged eyeball (6% vs 14%; p=0.004), decreased vision (3% vs 11%; p=0.0002), and eyelid swelling (2% vs 8%; p=0.0008) were more common in group 2. Extraocular tumor extension was less common in group 1 compared to group 2 (8% vs 18%; p=0.0009). Based on the 8th edition of American Joint Committee Classification, T2 was more common in group 1 (56% vs 22%; p=0.0001), while T3 (14% vs 41%; p=0.0001) and T4 (12% vs 23%; p=0.001) were more common in group 2. The most common primary treatment modality was intravenous chemotherapy in group 1 (61% vs 39%; p=0.0001) and enucleation (33% vs 55%; p=0.0001) in group 2. Compared to group 2, group 1 had better chances of globe salvage (54% vs 31%; p=0.0001) and life salvage (93% vs 81%; p=0.0001) over a mean follow-up period of 41 months (median, 27 months; range, <1 to 308 months) in group 1 and 42 months (median, 21 months; range, <1 to 231 months) in group 2.

Conclusion: Atypical presenting features and advanced retinoblastoma are more common in older children. Life and globe salvage rates are better in younger children than those presenting at an older age with retinoblastoma.

Retinoblastoma (RB) is predominantly a disease of the young children and is rarely detected in late childhood.1 Retinoblastoma in adults is further uncommon.2 There is an association between age at presentation and tumor features including laterality, tumor stage, and pathological grade,3 which could influence the overall survival of RB patients.

Younger RB patients tend to have bilateral affection, smaller tumors, and low-grade tumors,3 while older children have sporadic unilateral tumors and are often misdiagnosed due to atypical clinical features.4-9 Comparative genomic hybridization in RB tumor samples also revealed differences based on age at operation, with older children exhibiting significantly more frequent and more complex genetic abnormalities compared to younger children, suggesting that RB progression in older children follows different mutational pathways compared to younger children.10 Herein, we study the differences in clinical presentation, tumor staging, treatment, and outcome of RB based on the age at diagnosis.

Methods:

Institutional Review Board approval was obtained for this retrospective comparative study. It included all RB patients up to the age of 20 years, who had presented to the Operation Eyesight Universal Institute for Eye Cancer, LV Prasad Eye Institute, Hyderabad, India from 2000 to 2015. All patients with inadequate data or aged > 20 years at presentation were excluded from the study.

Age, gender, and family history of RB were recorded. Presenting complaints, tumor laterality, and tumor features were recorded. Intraocular tumors were categorized based on the International Classification for Intraocular retinoblastoma (ICIoR).11 All tumors were classified based on International Retinoblastoma Staging System (IRSS) 12 and the 8th edition of American Joint Committee Classification (AJCC).­13

Depending on the stage at presentation, appropriate primary treatment (transpupillary thermotherapy, cryotherapy, systemic chemotherapy, external beam radiotherapy, or enucleation) was planned. Secondary treatment details were also recorded. Histopathology features of enucleated eyes were recorded. Outcomes including globe salvage, metastatic spread, and survival were noted.

Statistical analysis:

Based on the age at presentation, the patients were divided into 2 groups, group 1 comprising of patients < 5 years and group 2 including patients aged >5 to 20 years. The demographic features, clinical features, treatment, and outcome between the two groups were compared. Statistical test was performed using t-test for parametric data and Yates corrected Chi-square/two-tailed Fisher exact test for non-parametric data. Statistical significance was defined as p-value <0.05.

Results:

The demographic data is listed in Table 1. The median age at diagnosis of retinoblastoma in group 1 was 23 months and in group 2 was 79 months. Though unilateral involvement was common in both groups, bilateral affection was more common in group 1 compared to group 2 (44% vs 22%; p=0.0001). The most common presenting complaints in both groups was leukocoria. However, on comparison of group 1 versus group 2, leukocoria (77% vs 54%; p=0.0001) was the more common in group 1, while proptosis/enlarged eyeball (6% vs 14%; p=0.004), decreased vision (3% vs 11%; p=0.0002), and eyelid swelling (2% vs 8%; p=0.0008) were more common in group 2. Initial misdiagnosis was common in group 2 (<1% vs 7%; p=0.0001) including endophthalmitis (n=3), trauma related hyphema and vitreous hemorrhage (n=1), Coats disease (n=1), retinal detachment (n=1), and panophthalmitis (n=1).

Extraocular tumor extension was less common in group 1 compared to group 2 (8% vs 18%; p=0.0009). Based on ICIoR, groups C (7% vs 2%, p=0.03) and D (22% vs 16%, p=0.05) were more common in group 1 compared to group 2. Based on IRSS, stage 0 (46% vs 23%, p=0.0001) was common in group 1, while stage 1 (44% vs 58%; p=0.004), stage 3 (6% vs 11%; p=0.03), and stage 4 (2% vs 7%; p=0.01) were more common in group 2. Based on the 8th edition of AJCC, T2 was more common in group 1 (56% vs 22%; p=0.0001), while T3 (14% vs 41%; p=0.0001) and T4 (12% vs 23%; p=0.001) were more common in group 2 (Table 2).

Treatment and outcome in both groups is listed in table 3. The most common primary treatment modality was intravenous chemotherapy in group 1 (61% vs 39%; p=0.0001) and enucleation (33% vs 55%; p=0.0001) in group 2. Over a mean follow-up period of 41 months (median, 27 months; range, <1 to 308 months) in group 1 and 42 months (median, 21 months; range, <1 to 231 months) in group 2, group 1 had better chances of globe salvage (54% vs 31%; p=0.0001) and life salvage (93% vs 81%; p=0.0001) compared to group 2.

Discussion:

Worldwide, 95% RB cases are detected before the age of 5 years. In a recent analysis of Surveillance, Epidemiology, and End Results from the United States of America including 879 RB cases over a 40-year period, 84% were between the age of 0 and 3 years, and 16% between 3 and 9 years, with 96% cases diagnosed before the age of 4 years.14 In a study of 1609 cases of RB from UK, 1525 (95%) were aged below 5 years, and 76 (5%) were beyond the age of 5 years.15 The occurrence of RB in older children (>5 years) is less common with a reported incidence of 4% to 9%.4,7,8,9,16 In this series of 1450 patients with RB, 93% were below the age of 5 years and only 7% were above the age of 5 years.

The most common presenting complaints of RB are leukocoria and strabismus,17 though proptosis or fungating mass are more common in certain regions of Africa and Asia.18,19 In younger children, these findings are more commonly picked up by parents or family members. However, atypical symptoms including decreased vision, pain, and floaters are more common in older children.4-9, and usually the child notices the symptom(s) first rather than parents or family members. In an analysis of 24 cases of RB in older children, the child noticed the symptom(s) first in 83% cases.9 In our series, though leukocoria was the most common symptom in both younger and older children group, the atypical symptoms of proptosis, decreased vision, and eyelid swelling were more common in older children. Leukocoria was more common in younger children compared to older children.

In most cases of retinoblastoma, the diagnosis can be established by a good clinical examination, which usually reveals a yellowish-white retinal mass with a feeder vessel dipping into the lesion, with/without associated vitreous seeds, subretinal seeds, and subretinal fluid. However, atypical signs including hypopyon, hyphema, vitreous hemorrhage, or orbital pseudo cellulitis are more frequently evident in older children leading to misdiagnosis as uveitis or endophthalmitis, and thus resulting in inadvertent intraocular surgery.6,9,20 The rate of misdiagnosis in older children with RB is 23 to 31%.4,7-9 In our series, the rate of misdiagnosis in older children with RB was 7%, against <1% in younger children. The most common misdiagnosis included endophthalmitis (3%) in our series.

Unilateral affection of RB is seen in 59% cases, while 41% have bilateral involvement.17 Similarly, in our study, 56% of younger patients had unilateral tumor and 44% had bilateral involvement. Unilateral affection of RB is much more common in older patients accounting for 78% to 100% cases.4,8,9 Most older children with RB have a negative family history of RB suggesting sporadic occurrence of tumor. In our study, 22% had bilateral involvement, which was significantly lower than the younger patient group. There was a known family history of RB in 3% cases, most commonly in younger siblings.

In our series, younger children presented more often with T1 or T2 tumors, while older children frequently presented with T3 or T4 tumors. Extraocular extension of RB was more common in older children compared to younger children. This suggests delayed diagnosis and advanced disease in older children at presentation. This could be related to initial misdiagnosis and lower chances of suspicion of RB in older children. This eventually resulted in lower chances of globe salvage and life salvage in older children compared to younger children. With the advent of newer treatment modalities, the globe salvage rates have significantly improved for RB. However, due to delayed presentation with advanced tumors in older children, the globe salvage rates are reported at only 8% in EBRT era9 and 6% to 38%4,7,8 in chemotherapy era. In our series, the globe salvage rate was 31% in older children versus 54% in younger children. The overall survival of patients with retinoblastoma has also improved to >90% in developed countries and most developing countries. In older children with RB, the reported life salvage rates are 85% in EBRT era9 and 94%7,8 in chemotherapy era. Death is more common in children with a prior history of inadvertent intraocular procedure prior to the diagnosis of retinoblastoma. In our study, life salvage was achieved in 81% cases of older children compared to 93% cases of younger children. Of the 18 older children who died, 3 had undergone prior intraocular surgery and 10 had extraocular extension of RB on presentation.

In conclusion, retinoblastoma occurs less commonly in older children. Compared to younger children, older children with RB have poorer chances of globe and life salvage due to advanced disease at diagnosis. Increased suspicion of RB in older children with atypical signs and symptoms may decrease the chances of misdiagnosis, delayed diagnosis, inadvertent intraocular surgeries, and thus increase the chances of globe and life salvage.

References:

1. Broaddus E, Topham A, Singh AD. Incidence of retinoblastoma in the USA:1975-2004. Br J Ophthalmol 2009;93(1):21-3.

2. Kaliki S, Shields CL, Gupta A, et al. Newly diagnosed active retinoblastoma in adults. Retina 2015;35(12):2483-8.

3. Andreoli MT, Chau FY, Shapiro MJ, Leiderman YI. Epidemiological trends in 1452 cases of retinoblastoma from the Surveillance, Epidemiology, and End Results (SEER) registry. Can J Ophthalmol 2017;52(6):592-598.

4. Chang Y, Shi J, Zhao J, et al. Retinoblastoma in Chinese children aged five to fourteen years. Ophthalmologica 2015;233(3-4):222-9.

5. Sheck LH, Ng YS, Watson M, Vincent AL. Clinical findings and molecular diagnosis of retinoblastoma in older children. Ophthalmic Genet 2013;34(4):238-42.

6. All-Ericsson C, Economou MA, Landau I, Träisk F, Seregard S. Uveitis masquerade syndromes: diffuse retinoblastoma in an older child. Acta Ophthalmol Scand 2007;85(5):569-70.

7. de Aguirre Neto JC, Antoneli CB, et al. Retinoblastoma in children older than 5 years of age. Pediatr Blood Cancer 2007;48(3):292-5.

8. Karcioglu ZA, Abboud EB, Al-Mesfer SA, Al-Rashed W, Pilapil DH. Retinoblastoma in older children. J AAPOS 2002;6(1):26-32.

9. Shields CL, Shields JA, Shah P. Retinoblastoma in older children. Ophthalmology 1991;98(3):395-9.

10. Herzog S, Lohmann DR, Buiting K, et al. Marked differences in unilateral isolated retinoblastomas from young and older children studied by comparative genomic hybridization. Hum Genet 2001;108(2):98-104.

11. Shields CL, Mashayekhi A, Demirci H, Meadows AT, Shields JA. Practical approach to management of retinoblastoma. Arch Ophthalmol 2004;122:729-35.

12. Chantada G, Doz F, Antoneli CB, Grundy R, Clare Stannard FF, Dunkel IJ, et al. A proposal for an international retinoblastoma staging system. Pediatr Blood Cancer 2006;47(6):801-5.

13. Mallipatna AC, Gallie BL, Chévez-Barrios P, et al. Retinoblastoma. In: Amin MB, Edge SB, Greene FL, eds. AJCC Cancer Staging Manual 8th ed. New York, NY: Springer; 2017:819-831.

14. Fernandes AG, Pollock BD, Rabito FA. Retinoblastoma in the United States: A 40-Year Incidence and Survival Analysis. J Pediatr Ophthalmol Strabismus 2018;55(3):182-188.

15. MacCarthy A, Birch JM, Draper GJ, et al. Retinoblastoma in Great Britain 1963-2002. Br J Ophthalmol 2009;93(1):33-7.

16. Kaliki S, Patel A, Iram S, Ramappa G, Mohamed A, Palkonda VAR. Retinoblastoma in India: Clinical Presentation and Outcome in 1,457 Patients (2,074 Eyes). Retina 2017 Nov 23. [Epub ahead of print]

17. Abramson DH, Frank CM, Susman M, et al. Presenting signs of retinoblastoma. J Pediatr 1998;132:505-508.

18. Sah KP, Saiju R, Roy P, Kafle S. Retinoblastoma: ten years experience at Kanti Children’s Hospital. JNMA J Nepal Med Assoc 2013;52:576-579.

19. Owoeye JF, Afolayan EA, Ademola-Popoola DS. Retinoblastoma--a clinico-pathological study in Ilorin, Nigeria. Afr J Health Sci 2006;13:117–123.

20. Tuncer S, Peksayar G, Kebudi R, Tugal-Tutkun I, Buyukbabani N, Darendeliler E. Multiple anterior and posterior chamber pseudocysts in a 12-year-old boy with diffuse infiltrating retinoblastoma. J Pediatr Ophthalmol Strabismus 2009;46(5):312-6.