The Incidence of Binocular Visual Impairment and Blindness in Children with Bilateral Retinoblastoma

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Keywords

Retinoblastoma · Visual impairment · Blindness

Abstract

Purpose: The study aimed to assess the incidence of and risk factors leading to visual impairment and legal blindness in children with retinoblastoma. **Procedures:** This is a single-center, retrospective case series of all patients with bilateral retinoblastoma presenting from 2010 to 2014. **Results:** A total of 44 patients were included in the study. Visual impairment was present in 14 (38%) children, legal blindness was present in 7 (19%) children. Bilateral macular tumors (BMT) were associated with visual impairment (12 of 18 patients with BMT, 2 of 19 patients without BMT, $p = 0.0006$) and legal blindness (7 of 18 patients with BMT, 0 of 19 patients without BMT, $p = 0.003$). The International Intraocular Retinoblastoma Classification (IIRC) of the better eye also predicted visual impairment (16% in IIRC Group A–C, 75% in IIRC Group D, E, $p = 0.004$) and blindness (3% eye in IIRC Group A–C, 50% in Group D, E, $p = 0.005$). Various non-Snellen visual acuity measures were able to predict visual impairment in pre-ver-

bal children, providing them with early assistance. **Conclusions:** The rates of visual impairment and blindness reported in this paper can be used to counsel families regarding the risk of binocular visual impairment. Early detection and support for visually impaired infants are essential as development can be affected by severe visual impairment.

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Introduction

The treatment of retinoblastoma has evolved rapidly over the past 2 decades. Whereas external beam radiotherapy (EBRT) and enucleation were the mainstay of treatment throughout much of the twentieth century, globe salvage therapies and chemotherapy are now wide-

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ly used. Advances in primary systemic chemotherapy [1, 2], intra-arterial chemotherapy (IAC) [3, 4], and intravitreal chemotherapy [5] have provided a means of maintaining very low rates of metastatic disease while simultaneously leading to marked improvements in globe salvage rates. With more eyes being saved, the retinoblastoma specialist must now also consider long-term visual outcomes when choosing therapies and counselling families. In patients with bilateral disease, there is a risk not just of decreased visual acuity but of long-term binocular visual impairment and blindness. Monocular visual acuities of patients with bilateral retinoblastoma have been reported in the age of EBRT [6, 7] and recently in the age of chemotherapy [8, 9]. However, the incidence of visual impairment, a binocular calculation, in patients with retinoblastoma has not been previously reported. Subsequently, there are few data on the timing and use of visual rehabilitation programs in these young children.

Counselling patients with newly diagnosed, bilateral retinoblastoma can be challenging. While discussing the necessary curative options for the child, it can be difficult to focus on long-term visual prognosis, but this is an important concern for care-givers. Parents and care-givers are concerned both with the new diagnosis of cancer as well as for the visual potential for their child. Parents' concerns are well-founded; bilateral retinoblastoma can be associated with severe visual impairment and this can profoundly affect the development of infants and children [10–12]. The incidence of visual impairment and blindness is information that can be easily understood by all during these initial conversations. This study addresses the incidence of visual impairment in children with bilateral retinoblastoma. The variable of interest is not monocular visual acuities but whether or not children meet the criteria for binocular visual impairment or legal blindness.

Materials and Methods

The retrospective study was approved by the Barts Health Clinical Effectiveness Unit (#5538) and followed the tenets of the Declaration of Helsinki. This was a retrospective case series of children presenting with bilateral retinoblastoma to the Retinoblastoma Unit at the Royal London Hospital, UK, between 2010 and 2014. Unilateral retinoblastoma would not lead to vision impairment nor legal blindness due to 1 eye being spared, so these patients were excluded. Data were collected on demographic characteristics, date of diagnosis and treatment, type of therapy, and vision testing. Clinical retinal drawings or fundus photos were used to determine the location of the tumors. Eyes were categorized using the International Intraocular Retinoblastoma Classification

(IIRC) [13]. The initial treatment for all patients was the same, systemic chemotherapy in the form of 6 cycles of carboplatin, vincristine, and etoposide. Adjuvant treatments including EBRT, plaque brachytherapy, cryotherapy, and laser were used as deemed necessary by the senior ophthalmologists (M.S.S. and M.A.R.). IAC and intravitreal chemotherapy were used as salvage treatments in cases where the tumor and/or tumor seeds had failed to respond to other treatments.

All patients underwent orthoptic examinations, cover testing, and investigation into binocular vision. In younger and preverbal children, visual acuities were recorded as grating visual acuities using Cardiff Cards, Keeler Cards, Kays optotypes, or similar. Crowded logMAR charts and Snellen acuity were used in older children. If quantitative methods were not possible, qualitative methods were used, namely fixing and following a target or identifying a fixation preference [14]. The results of these routine assessments are the subject of this study.

To determine legal blindness and visual impairment based on Snellen visual acuities, the following acuity thresholds were used: visual impairment is Snellen acuity between 20/40 (logMAR: 0.3) and 20/200 (logMAR: 1.0) in the better eye, legal blindness is vision of 20/200 or worse in the better eye. These thresholds are followed by most governing bodies including the World Health Organization and Centers for Disease Control [15]:

The patients in this cohort were registered through the UK Certificate of Visual Impairment system where patients were identified Sight Impaired or Severely Sight Impaired. The guidelines for the UK registration are more open to individual case interpretation, but generally follow the partitions listed above. The age of the patient as well as the time since diagnosis were recorded on the date of Certificate of Visual Impairment registration for all patients.

Clinical comparisons and statistical analysis were completed using the R Statistical Package [16]. An alpha level of 0.05 and 2-tailed *p* values were used to determine statistical significance. Correction for multiple comparisons was not required. Wilcoxon rank sum test was used to analyze non-parametric data, Fisher-exact test was used for categorical comparisons, and Student's *t* tests were used for comparison of continuous data. A Kaplan-Meier estimator was used to estimate the time between presentation and registration as vision impaired.

Results

A total of 44 patients presented with bilateral retinoblastoma during the dates of inclusion for the study. An equal number of these patients were men (22) and women (22). The median age of presentation was 9 months (range 0.25–103 months). The median follow-up time was 33 months (range 4–63 months). The disease was sporadic in 37 patients (84%), while the remaining 7 patients (16%) had familial disease. Of the sporadic cases, the median age at presentation was 10 months (range 1–103 months). Of the familial cases, the median age of presentation was 0.33 months (range 0.25–10 months).

Table 1. Demographic data and retinoblastoma tumor characteristics of all patients in the study

Overall	
Number of patients, <i>n</i>	44
Number of eyes, <i>n</i>	88
Males, <i>n</i> (%)	22 (50)
Females, <i>n</i> (%)	22 (50)
Age at presentation, months, median (range)	9 (0.25–103)
Follow-up, months, median (range)	33 (4–63)
Sporadic disease	
Number of patients, <i>n</i> (%)	37 (84)
Median age at presentation, months, median (range)	10 (1–103)
Familial disease	
Number of patients, <i>n</i> (%)	7 (16)
Median age at presentation months, median (range)	0.33 (0.25–10)
Presenting (IIRC) group, <i>n</i> (%)	
A	15 (17)
B	17 (19)
C	9 (10)
D	25 (28)
E	22 (25)
Group (IIRC) of better eye, <i>n</i> (%)	
A	13 (30)
B	12 (27)
C	7 (16)
D	10 (23)
E	2 (5)
Macular tumors, <i>n</i> (%)	
Eyes with macular tumors	65 (74)
Patients with bilateral macular tumors	22 (50)
Patients with unilateral macular tumors	21 (48)
Patients with no macular tumors	1 (2)
Number of visually impaired children based on the presenting IIRC group of the better eye, <i>n</i> (%)	
A	1/11 (9)
B	2/9 (22)
C	2/6 (33)
D	7/9 (78)
E	2/2 (100)
Number of legally blind children based on the presenting IIRC group of the better eye, <i>n</i> (%)	
A	0/11 (0)
B	1/9 (11)
C	0/6 (0)
D	5/9 (56)
E	1/2 (50)

The presenting IIRC groups of the 88 affected eyes are demonstrated in Table 1. The patients were then grouped based on the IIRC classification of the better eye (Table 1). A macular tumor was found in 65 eyes (74%). A total of 22 patients (50%) had macular tumors in both eyes, 21 patients had macular tumors in 1 eye, and 1 patient had no macular tumors.

All patients underwent systemic chemotherapy with 6 cycles of a 3-drug protocol: vincristine, etoposide, and

carboplatin. If a patient with bilateral retinoblastoma presented with 1 Group E eye, it was treated with primary enucleation in combination with the systemic chemotherapy. If a child presented with bilateral Group E eyes (2 children, 5% of bilateral cases), the clinically more advanced eye was enucleated primarily, the child was treated with systemic chemotherapy, and the other eye was monitored closely. A total of 23 eyes (26%) were enucleated; 17 eyes enucleated primarily and 6 were enucleated

Fig. 1. Box plots of final visual acuity (logMAR) of each eye based on presenting IIRC group classification (1 response for each eye). This graph ignores enucleated eyes. Therefore, the following categories are missing enucleated eyes: “C” (1 eye), “D” (4 eyes), “E” (18 eyes). Also note, “Perception of Light” was grossly estimated with a logMAR acuity of 3.0.

Fig. 2. Box plots of final visual acuity (logMAR) of the better eye based on presenting IIRC group classification of the BETTER eye (1 response for each patient). Patients with bilateral enucleation cannot provide any visual acuity and are represented with black dots in their respective categories (2 patients). Patients with visual acuity of 20/200 or worse in the better-seeing eye are considered legally blind. This line is represented by the dotted line at logMAR = 1.0. Patients with visual acuity of 20/40 or worse in the better eye are considered visually impaired. This line is represented by the dashed line at logMAR = 0.4.

after failing to respond to treatments. Of the enucleated eyes, most were from Group E (18, 82%). There were no enucleated eyes from Groups A or B; 1 Group C eye (11% of Group C eyes) was enucleated and 4 Group D eyes (16%) were enucleated. Nineteen children underwent unilateral enucleation (43% of patients) while 2 children (5%) underwent bilateral enucleation. Nineteen eyes (22%) underwent adjuvant IAC, with 3 children (5%) undergoing IAC in both eyes. The majority of eyes treated with IAC underwent 3 treatments (9 of 19 eyes, range 1–7 treatments). Laser treatment was used in 40 eyes (45%), while cryotherapy was used in 47 eyes (53%). Cataract surgery was required in 1 eye. Ruthenium plaque radiotherapy was required in 2 eyes. EBRT was performed in 5 eyes as a salvage treatment, with 1 patient undergoing EBRT to both eyes. Second-line systemic chemotherapy (ifosfamide, vincristine, and doxorubicin) was required in 3 patients.

The monocular visual acuity at the most recent follow-up was recorded for each eye in each patient. Snellen as well as grating visual acuities were converted to a logMAR equivalent where possible. The average visual acuities in each IIRC group were as follows: Group A (logMAR median 0.1), Group B (median 0.1), Group C (median 0.2), Group D (median 1.2), and Group E (median 1.3, $p = 0.000002$, Fig. 1). Previously enucleated eyes were omitted from this analysis as they could not provide a visual acuity. Eyes with tumors presenting in the macula demonstrated worse long-term visual potential (median logMAR = 0.90) than peripheral tumors (median logMAR = 0.05, $p = 0.000007$). There was no significant correlation between visual acuity and laser therapy ($p = 0.946$), IAC ($p = 0.199$), cryotherapy ($p = 0.42$), plaque radiotherapy ($p = 0.99$), EBRT ($p = 0.70$), or with need for second-line chemotherapy ($p = 0.18$).

At the last follow-up visit, 7 children were unable to provide objective logMAR visual acuities due to age. The visual acuity of the better eye in the remaining 37 children was calculated and are demonstrated as a function of IIRC classification in Figure 2. Of these 37 patients, 23 (62%) had no visual impairment. A total of 14 patients (38%) met the criteria for visual impairment and 7 children (19%) met the criteria for legal blindness.

The presence of visual impairment or legal blindness was compared to possible cofactors that affect both eyes (sporadic vs. familial disease, age at diagnosis, IIRC classification of better eye, second-line chemotherapy, presence of bilateral macular tumors (BMT), use of IAC bilaterally, use of laser bilaterally). Of these variables, only the IIRC classification of the better eye and the presence of

Fig. 3. Kaplan-Meier curve representing the time to visual impairment registration.

BMTs were both found to significantly correlate with both visual impairment and legal blindness. Worse IIRC group classification of a patient's better eye is predictive of higher rates of vision impairment: Group A had a 9% rate of visual impairment, Group B: 22%, Group C: 33%, Group D: 78%, Group E: 100% (difference between groups, $p = 0.004$, Table 1). Similarly, patients with better eye classified as IIRC Group A had a 0% rate of legal blindness, Group B: 11%, Group C: 0%, Group D: 56%, Group E: 50% (difference between groups, $p = 0.005$, Table 1). It should be noted that the child who presented with a Group A eye and developed vision impairment was a child with familial disease and was diagnosed with bilateral Group A/B retinoblastoma at age of 11 days. She went on to develop additional tumors in her macula after diagnosis which left her with 20/50 (logMAR 0.4) vision in the better eye.

When Groups A–C eyes and Groups D and E eyes were combined, the data demonstrated a significant difference between the 2 groups. A total of 19% (5 of 26) of patients with a better eye in IIRC Groups A–C met the criteria for visual impairment while 82% (9 of 11) of patients with a better eye in IIRC Groups D and E met the criteria for visual impairment ($p = 0.0006$). Similarly, patients with a better eye in IIRC Groups A–C met criteria for legal blindness 4% (1 of 26 patients) of the time while patients with a better eye in IIRC Groups D and E met the criteria for legal blindness 55% of the time (6 of 11 patients, $p = 0.001$).

The presence of BMTs was highly correlated with visual impairment and blindness. Visual impairment was

more likely in patients with bilateral tumors (67%, 12 of 18 patients) compared to patients without BMTs (11%, 2 of 19 patients, $p = 0.0006$). Likewise, legal blindness was more likely in patients with bilateral tumors (39%, 7 of 18 patients) than in patients without BMTs (0 of 19 patients, $p = 0.003$). Nearly all patients who met the criteria for visual impairment (86%, 12 of 14 patients), and every single patient who met the criteria for legal blindness (100%, 7 of 7 patients) presented with BMTs. It should be noted, however, some patients who presented with bilateral macular disease maintained good vision (>20/40 in better eye, 33%) and many maintained ambulatory binocular vision (>20/200 in the better-seeing eye, 61%).

The results of the 7 patients with familial retinoblastoma were compared to those with sporadic retinoblastoma. Familial cases presented at a median of 13 days (range 8 days, 32 months) compared to sporadic cases which presented at a median of 9.5 months (range 1–103 months). There was no statistical difference between the age of the 2 groups ($p = 0.22$). The visual results were also similar between the groups: the median logMAR visual acuity of the better-seeing eye at last follow-up in familial cases was 0.3 (range 0.1–3.0) compared to sporadic cases with a median of 0.2 (range –0.1 to 1.3, $p = 0.33$). Visual impairment was seen in 3 of 7 (43%) patients with familial disease compared to 11 of 29 (38%) of patients with sporadic disease ($p = 0.99$). Similarly, blindness was seen in 2 of 7 (29%) patients with familial disease compared to 5 of 29 (17%) of patients with sporadic disease ($p = 0.60$).

As of the last follow-up, a total of 14 patients (32%) had been registered with the national visual impairment authority. Some patients in the series have applied for registration and applications were pending at the time of the last follow-up. The median age at registration was 22 months (range 3–48 months). The timing of registration for government services was recorded in each case. A Kaplan-Meier survival curve was calculated to demonstrate the time from diagnosis to registration for all patients in the series as well as to estimate the expected rate of visual impairment registration in the study (Fig. 3). The majority of patients were registered within the first year after diagnosis and this facilitates assessment by a visual rehabilitation specialist.

Discussion

There has been a recent paradigm shift in the treatment of retinoblastoma with new treatment techniques involving chemotherapy leading to more salvaged eyes.

It is important to assess the impact of new treatments on vision so that accurate advice can be given to parents. With many new treatment options, patients are often exposed to several different treatment modalities, as is the case in this heterogeneous patient cohort. There are a number of reports of the visual acuities of patients with bilateral retinoblastoma. However, incidence of binocular visual impairment has not previously been reported.

These data have their limitations due to the retrospective nature of the data, the short follow-up in some of the more recent patients, and the fact that patients underwent many diverse treatments. Nevertheless, these data provide important information for retinoblastoma specialists and care-takers. It is well documented that IIRC group classification and the presence of macular tumors can be predictive of long-term visual acuities in retinoblastoma; the data in this study now also demonstrate that these same 2 factors are predictive of a patient's future visual impairment and/or legal blindness, entities that are much easier to understand. The simple incidence rates reported here can be used when counselling families. If the better eye of a patient with newly diagnosed, bilateral retinoblastoma is Group A, B, or C, the probability of visual impairment is 19%, with 81% avoiding visual impairment. Likewise, if the better eye is in Group A, B, or C, the probability of legal blindness is 4%, with 96% of patients avoiding legal blindness. With regard to macular tumors, in this series, no child progressed to legal blindness in the absence of BMTs and only 12% of these patients developed visual impairment. The presence of BMTs does not necessarily portend a poor vision long-term. Of those patients who had BMTs, only 67% of them progressed to visual impairment and only 39% of them progressed to legal blindness. This information can be very important during family discussions and provides hope to those with children who have bilateral disease.

In this series, we see no difference in long-term binocular visual outcomes between patients with familial and sporadic disease. The visual acuity of the better-seeing eye, the rate of visual impairment, and the rate of legal blindness are similar between the 2 groups. In this series, there were only 7 familial cases and 1 was a patient who presented late at 10 months with bilateral Group D eyes and only light perception in each eye. These low numbers and outlier may affect the comparison between the familial and sporadic groups.

Previous studies assessing vision in children with retinoblastoma have delayed the assessment until children are verbal and can state their vision on a Snellen

chart. Such an approach may delay infants being identified as visually impaired and therefore receiving appropriate neuro-developmental support and will delay the reporting of visual outcomes when new treatment modalities are being used. Grating visual acuity, though the use of Cardiff cards or Teller cards, can provide enough evidence that patients are visually impaired. Likewise, a visual acuity examination in a preverbal child who fails basic vision exams (e.g., unable to fix and follow, etc.) can also provide enough evidence for early registration as visually impaired. Figure 3 demonstrates that most patients are registered as visually impaired within a year of their diagnosis and treatment. Earlier visual acuity testing in these children, through pre-verbal methods if necessary, can aid in more seamless access to resources.

There is a growing body of evidence that providing early support for visually impaired infants from any cause will provide life-long benefits and reduce developmental regression associated with severe visual impairment [10]. Furthermore, research suggests that 33% of children with profound visual impairment (light perception or worse) suffer from developmental setback in the second or third year of life [11]. Even children who have better vision (visual impairment) can have poor shifting attention capabilities between objects and non-visual techniques should be exploited to avoid plateauing of development or even regression [12]. Where available, early registration with government agencies devoted to visual impairment can provide patients and families with valuable resources. By assessing the vision as early as possible, visual impairment can be identified and visual rehabilitation will not be delayed.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to report.

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