Strabismus as a presenting sign in Retinoblastoma

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Abstract

PURPOSE
To report the presenting signs of Retinoblastoma (Rb) in a large cohort of patients who underwent orthoptic assessment at presentation.

METHODS
A retrospective medical chart review of 131 patients with retinoblastoma who presented consecutively to a single institution over a 6-year period. The main outcome measure was the presenting sign(s) of the disease.

RESULTS
Of 131 Rb patients, 88 presented with unilateral disease and 43 bilateral disease (mean age; 22.7 and 14.8 months respectively). Leukocoria (L) was the presenting sign in 56% of patients, leukocoria and strabismus (LS) in 18%, strabismus (S) in 13%, inflammation (I) in 8%, and ‘other’ signs in 5%. The fovea was affected by the Rb tumor or its sequelae in 75% of cases. Patients who presented with strabismus were significantly more likely to have foveal involvement than patients who presented with leukocoria alone (P = 0.001). 31% of patients had strabismus as a component of their presentation; 63% had exotropia, 23% had esotropia, and 14% had variable strabismus. The percentage of patients with strabismus rises to 66% if small angle and variable strabismus is also considered. Patients with inflammation had worse ocular survival (P <0.05).

CONCLUSIONS
The combination of leukocoria and strabismus as presenting features of Rb has been assessed. Foveal involvement is common in patients who have strabismus and may influence decision-making regarding globe salvage. We have confirmed that exotropia is more common than esotropia in Rb in the largest cohort to have undergone an orthoptic assessment.
Introduction

Retinoblastoma (Rb) is the most common pediatric intraocular cancer, occurring in 1:16,000-18,000 live births (1). Patient and ocular survival largely depend upon disease severity at presentation. In high-income countries (HIC), where survival rates are as high as 97-100% at 5 years (2), the main treatment challenges are eye salvage and preservation of vision, which depend on early tumor detection. In low-income countries (LIC) early detection may be lifesaving. In a recent global study, it was shown that patients from HICs were diagnosed at a median age of 14.1 months and 98.5% had intraocular disease. Patients from low-income countries were diagnosed at a median age of 30.5 months; 49.1% had extraocular retinoblastoma. Older age at presentation and low-income level were shown to be independent risk factors for advanced disease (3). In the UK our group has shown that ethnicity and socioeconomic status do not increase the risk of presenting with advanced disease, likely due to equality of access to healthcare (4). Regardless, early detection is of utmost importance.

The signs and symptoms of patients presenting with intraocular Rb in high-income countries are well documented. Studies from Europe and the United States have been consistent in showing that patients most commonly present with leukocoria (50-60%), strabismus (20-25%), or inflammation (6-10%) (5-8). Presenting signs have been shown to correlate with ocular survival; Abramson et al. (9) have reported improved ocular survival in patients presenting with strabismus compared to leukocoria.

The landscape of Rb diagnosis and management has changed; referral pathways, physician and patient education (10-12), diagnostic methods, disease classification, and treatment have evolved (13). At the Royal London retinoblastoma service an important change in practice over the last decade has been the introduction of an orthoptic assessment for all patients at presentation. This has led to improved detection and classification of strabismus in patients with Rb (14,15).

The aim of this study was to revisit the presenting signs of Rb in the context of current best practice with respect to diagnosis and assessment of the disease. It is hypothesized that detailed stratification of presenting signs is facilitated by formal orthoptic assessments at the time of presentation. This will better inform the nature of strabismus in retinoblastoma.
Patients and Methods

This was a retrospective medical chart review of 131 consecutive cases, excluding those with a positive family history, referred to our institution between 2009 and 2015. The study was approved by the National Research Ethics Committee (Reference 11/LO/0981). This research adhered to the tenets of the Declaration of Helsinki. Letters from referring physicians were analyzed to determine the reason for referral. Medical charts were evaluated to ascertain the signs of the disease at presentation to our center. All patients underwent examination under anesthetic (EUA) after initial presentation. Data collected included sex, age at diagnosis, presenting sign, disease laterality, and tumor group according to the International Intraocular Retinoblastoma Classification (IIRC) (16).

Orthoptic Assessment

Orthoptic assessments at presentation to our center were evaluated to determine the presence of strabismus. Orthoptic evaluation occurred before the first examination under anesthesia and included visual behaviour assessment; cover test at near (1/3m) and distance (6m); binocular function testing in those with aligned eyes, including motor fusion and stereopsis assessment using the Frisby Near Stereotest (Stereotest Ltd, Sheffield, UK); ocular motility examination, including convergence and smooth pursuit assessment; nystagmus assessment; and, where possible, measurement of ocular deviation using prism cover testing or prism reflection testing in cases of poor visual acuity or fixation. In cases where strabismus was variable, a measurement was not possible. Strabismus was considered for a constant tropia rather than a phoria.

Classification of Presenting Signs

Presenting signs were grouped as follows: leukocoria, leukocoria and strabismus, strabismus, inflammation, inflammation and strabismus. For the purposes of this study, patients who presented to their referring physician with a sign other than strabismus were denoted as having strabismus only if their angle of deviation measured ≥15 prism dioptres, or a ‘moderate’ strabismus or worse was documented at orthoptic assessment. Patients who presented with strabismus alone to their referring physician were labelled as presenting with strabismus regardless of the size of their deviation; strabismus measurement criteria were not applied to these patients as this was the only sign noted in their presentation.

Data were entered into Excel version 16.0 (Microsoft Corp., Redmond, WA, USA) and SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) was used to analyze all data. Categorical variables were compared with Chi-squared test. The statistical significance level was set at 0.05. Data throughout is presented as medians.

Results

Presenting Features

Of the study cohort, 88 (67%) patients presented with unilateral retinoblastoma, and 43 (33%) with bilateral disease (174 eyes in total). The median age at presentation was 16 and
10 months respectively. Sex was female in 65 patients (49.6%) and male in 66 patients (50.4%) (Table 1).

Of the study cohort, 119 (91%) patients underwent a full orthoptic assessment at presentation. The most common examination findings of Rb were leukocoria only (L, n = 73, 56%), followed by leukocoria with strabismus (LS, n = 23, 18%), and strabismus (S, n = 17, 13%). Eleven (8%) patients presented with periocular inflammation (I). The remaining 6 (5%) patients presented with ‘other’ (O) signs and symptoms; iris color change, proptosis, floaters, nystagmus, and an incidental radiological finding of retinoblastoma. The ratios of patients presenting with L, LS, S or I were largely preserved between unilateral and bilateral disease except for in the strabismus group where there were a greater proportion of patients presenting with unilateral disease; 5:1 unilateral to bilateral presentations (Figure 1).

Strabismus

Strabismus was a component of the presentation in 40 (31%) patients; 17 presented with strabismus alone, 22 with leukocoria and strabismus, and one with inflammation and strabismus. With respect to the type of strabismus, 63% (n=25) of patients had exotropia, 23% (n=9) had esotropia, and 14% (n=6) had variable strabismus. In this series of patients exotropia was more common than esotropia by a factor of 3:1.

In patients who presented with strabismus in combination with another sign, strict criteria were used in classifying these patients as having strabismus (either a ‘moderate angle’ or ≥15 prism dioptres). These criteria were not applied to patients presenting with Strabismus.
alone, as it was there only presenting sign. Of the 17 patients who presented with strabismus alone, 5 had deviations that were smaller than 15 degrees or ‘moderate’ on orthoptic assessment, and 6 had a variable strabismus.

Small angle strabismus was a feature of 33 (25%) presentations in total in this series, with 24, three and one patients in the leukocoria, inflammation, and other groups respectively having a small angle strabismus. Furthermore, eight and six patients in the leukocoria and inflammation groups had a variable strabismus. If all strabismus is considered, regardless of the angle of measurement or variability, then 66% of patients presenting with Rb would be classified as having strabismus as a feature of their presentation; 53% of Rb patients would be classified as presenting with leukocoria and strabismus, 21% with leukocoria alone, and 13% with strabismus alone.

Nystagmus featured in 2 (1.5%) patients; in one case it was the presenting sign and in neither case was strabismus present.

**Foveal involvement**

The fovea was affected by the Rb tumor or its sequelae (retinal detachment) in 130 (75%) eyes included in the study. Of the 44 eyes where the fovea was not affected, 22 (50%) were the better staged eye in a patient with bilateral disease. In 3 bilateral patients where one eye did not have foveal involvement, the disease stage was the same in each eye. In only one case of bilateral disease the fovea was spared in both eyes; bilateral stage D. Of the 44 eyes with no foveal involvement, leukocoria was the presenting sign in 70% of cases. Of these patients, 53% had bilateral disease.

Patients presented with a combination of leukocoria and strabismus in 10% of cases where the fovea was not involved; all of these cases were bilateral, and the deviating eye was the fellow eye with the most advanced Rb stage (and foveal involvement). Of a total of 6 patients in the study who presented with ‘other’ signs and symptoms, 4 (66%) did not have foveal involvement; all cases were unilateral.

All but one patient who presented with strabismus had foveal involvement. The patient who had no foveal involvement presented with bilateral disease; the better, non-deviating eye’s fovea was spared. Patients who presented with Strabismus were significantly more likely to have foveal involvement than patients who presented with leukocoria (P = 0.001). Of the patients that presented with inflammation, 3 bilateral cases had foveal sparing in the better staged eye and 1 unilateral case did not involve the fovea.

In all cases of bilateral disease where the fovea was spared in the better (or equally) staged eye, the eye did not undergo primary enucleation. Of the 6 eyes with foveal sparing which underwent primary enucleation, all were cases of unilateral disease. The patient that presented with strabismus and no foveal involvement in their better eye did not undergo primary enucleation.

**Ocular Survival**

Of 131 presentations, 63% (n=83) underwent enucleation as their primary treatment, which reflects the high proportion of D and E eyes in the cohort (Table 1). 75% of patients who presented with Strabismus were enucleated compared with 51% of patients who presented
with leukocoria (P = 0.08). Combining all patients who had Strabismus as a feature of their presentation (LS and S), 69% underwent primary enucleation; this was not significantly higher than in patients presenting with leukocoria alone (P = 0.06).

Ocular survival was significantly poorer in patients presenting with inflammation than other signs (P = 0.02), with just one patient out of 12 avoiding primary enucleation. Of the 11 children who presented with inflammation and were enucleated, 50% received adjuvant chemotherapy, significantly more than if inflammation was not present (P = 0.005).

There was no significant difference in enucleation rates between patients presenting with unilateral disease (66%) and those presenting with bilateral disease (57%; p = 0.31) and enucleation relative to disease laterality did not differ significantly between groups (Table 1).

Enucleation rates in unilateral IIRC group D eyes fell during the study period; 10 out of 13 were enucleated between 2009 and 2012, compared to 1 out of 13 between 2013 and 2015.

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Table 1. Percentage and number (parenthesis) of patients who underwent primary enucleation vs globe-sparing therapy relative to IIRC presenting stage and disease laterality. Enuc: enucleation.
**Discussion**

The signs of leukocoria and strabismus may have been falsely dichotomized in previous descriptions of the presenting signs of Retinoblastoma. Major studies that have investigated the presenting signs of Rb vary in the time period over which data was collected; one Finnish study collected data from patients presenting between 1912 and 1964 (5), an English study; 1960-1970 (6), and two North American studies; 1960-1969 (7) and 1960-1990 respectively (8). Within each study, patient presentations were categorized according to a single presenting sign. Trincado et al. (18) reported that 2 out of their group of 41 patients sought medical attention due to both leukocoria and strabismus; their cohort did not undergo orthoptic assessments.

Our findings are consistent with previous studies in that 56% of patients presented with leukocoria alone, however it has been shown in this series that 18% of patients present with both leukocoria and strabismus. Larson and colleagues found that the threshold for observers to detect strabismus was 12.5 prism dioptries (19). As a result, criteria were applied in documenting the presence of Strabismus in patients with leukocoria (strabismus measuring either >15 PD or ‘moderate’ on orthoptic assessment). Strabismus findings in this group of patients were unlikely to be equivocal. Pediatric ophthalmologists are familiar with the presentation of ‘pseudo-strabismus’ due to broad epicanthic folds in an infant and orthoptic assessments allowed certainty in confirming the presence or absence of strabismus. The criteria applied in defining the presence of strabismus in patients with leukocoria also means that a conservative estimation of strabismus as a presenting sign in patients with Rb is presented in this study.

Detailed orthoptic assessments identify strabismus with a high level of accuracy. 90% of patients presenting to our unit underwent such an assessment, those that did not were clinically too difficult to be examined, all having presented with inflammation. Ideally all patients would have had quantitative measurements of their strabismus but given the age group and variation in co-operation this could not always be achieved.

It has been shown that exotropia is more common than esotropia in patients presenting with Rb by a factor of 3:1. Strabismus affects 2.1% of the population (20) and is normally expected to occur at a ratio of 3:1 eso- to exo-deviations (17). Previous studies have reported that esotropia was more common than exotropia in patients presenting with Rb (8). Patients with constant exotropia are more likely to have coexisting ocular or systemic disease (21).

The findings from our study demonstrate that Rb is consistent with this observation, and clinicians should be vigilant when assessing patients with constant exo-deviations. We have previously assessed the long-term results of strabismus and showed that at presentation 15 of 20 patients had an exotropia (13). This larger study confirms the ratio of eso:-exo-deviations in the Rb population at presentation and is relevant to all pediatric ophthalmologists who will be referred such patients.

The group of patients presenting with strabismus alone sheds further light on the subtlety of some strabismus presentations in Rb. Five of these 17 patients had small angle strabismus measuring less than 15 diopters, and 6 had variable strabismus, yet strabismus was their only sign at presentation. If all strabismus is considered, regardless of the angle of measurement or variability, then 66% of patients would be classified as having strabismus as a feature of
their presentation. Leucocoria with strabismus would be the most common presentation;
53% of patients. Strabismus may have been overlooked in patients presenting with
leukocoria in previous studies. The reverse is also possible however the authors feel that
Strabismus is harder to assess and has been less of a focus of Rb awareness campaigns; it is
more likely to have been missed in the past. Strabismus may be best evaluated by a
specialized orthoptist. Early detection of Rb in patients presenting with strabismus, in the
context of a high probability of foveal involvement, may be globe sparing. Physicians should
be alert to small angle deviations, and should be aware that exotropias of infancy are more
likely to confer pathology (21), retinoblastoma or otherwise.

Overall enucleation rates were lower in our data set than previous studies, reflecting changes
in diagnosis and treatment of Rb. Previous studies have captured data spanning wide time
points during which treatment paradigms have shifted. Enucleation, which was previously
the treatment of choice in advanced disease (22), has reduced in frequency since the
introduction of systemic, intra-arterial and intra-vitreal chemotherapy. Indeed, even within
the time course of this study, the enucleation rate in unilateral group D eyes has fallen
significantly due to changes in treatment approach.

Patients with Strabismus as a feature of their presentation had a trend towards higher rates of
enucleation than those presenting with leukocoria alone, but this did not reach significance.
Foveal involvement of the tumor or its sequelae is significantly higher in cases presenting
with Strabismus, confirming the findings of a previous study (8). The likelihood of globe
salvage may be influenced by tumor position, vision, and treatment decisions made together
with the families. In cases of poor visual potential, it is sometimes the case that families wish
to forgo the many examinations under anesthesia that would be required to salvage the eye
(23). Patients presenting with inflammation almost inevitably have advanced disease and the
probability of primary enucleation was 90% in this study.

Awareness campaigns are often focused on leukocoria however strabismus should not be
overlooked both in the context of public and physician education. Given that the presence of
strabismus may denote a higher incidence of foveal involvement, and a trend towards worse
ocular survival in Rb, accurate assessment of Strabismus is important and may be best carried
out by an orthoptist or a pediatric ophthalmologist within a multidisciplinary retinoblastoma
service. The detection of exotropia should alert healthcare professionals regarding
retinoblastoma.

The main limitation of this study is that quantitative visions are not reported. We attempted to
assess visions in these infants before their first examination under anesthesia. As they
attended *nil per os*, cooperation was often an issue; quantitative data was insufficient and as a
result has not been presented. Lag time or time to diagnosis was not assessed as we have
previously shown that in the UK, increased lag time was not associated with poorer outcomes
in terms of enucleation rates or adverse histopathology after enucleation (24). There has been
contradictory evidence regarding lag time and strabismus in South America (25,26). We
suspect the confusion has arisen due to the definition of strabismus which we have
standardized by the use of orthoptic assessments in the present study.

In conclusion, leukocoria and strabismus can occur at the same time in retinoblastoma.
These two signs may have been falsely dichotomized in the past and it is now understood that
many patients have a combination of both. We have confirmed that exotropia is more
common than esotropia at presentation in the largest cohort that has had an orthoptic
assessment. The angle of deviation may be small, and the presence of strabismus in
retinoblastoma may be considerably higher if small angle strabismus is considered. Specialist orthoptic assessment is recommended to assess retinoblastoma patients to accurately detect strabismus. We have also shown that foveal involvement is common in patients with Strabismus where early detection may be globe sparing. We believe this is important information for paediatric ophthalmologists and awareness campaigns that attempt to improve early detection.

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References


