

1 **Strabismus as a presenting sign in Retinoblastoma**

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33 **Abstract**

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35 **PURPOSE**

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

38 **METHODS**

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

42 **RESULTS**

43 Of 131 Rb patients, 88 presented with unilateral disease and 43 bilateral disease (mean age;
44 22.7 and 14.8 months respectively). Leukocoria (L) was the presenting sign in 56% of
45 patients, leukocoria and strabismus (LS) in 18%, strabismus (S) in 13%, inflammation (I) in
46 8%, and 'other' signs in 5%. The fovea was affected by the Rb tumor or its sequelae in 75%
47 of cases. Patients who presented with strabismus were significantly more likely to have
48 foveal involvement than patients who presented with leukocoria alone ($P = 0.001$). 31% of
49 patients had strabismus as a component of their presentation; 63% had exotropia, 23% had
50 esotropia, and 14% had variable strabismus. The percentage of patients with strabismus rises
51 to 66% if small angle and variable strabismus is also considered. Patients with inflammation
52 had worse ocular survival ($P < 0.05$).

53 **CONCLUSIONS**

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

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70 **Introduction**

71 Retinoblastoma (Rb) is the most common pediatric intraocular cancer, occurring in 1:
72 16,000-18,000 live births (1). Patient and ocular survival largely depend upon disease
73 severity at presentation. In high-income countries (HIC), where survival rates are as high as
74 97-100% at 5 years (2), the main treatment challenges are eye salvage and preservation of
75 vision, which depend on early tumor detection. In low-income countries (LIC) early
76 detection may be lifesaving. In a recent global study, it was shown that patients from HICs
77 were diagnosed at a median age of 14.1 months and 98.5% had intraocular disease. Patients
78 from low-income countries were diagnosed at a median age of 30.5 months; 49.1% had
79 extraocular retinoblastoma. Older age at presentation and low-income level were shown to
80 be independent risk factors for advanced disease (3). In the UK our group has shown that
81 ethnicity and socioeconomic status do not increase the risk of presenting with advanced
82 disease, likely due to equality of access to healthcare (4). Regardless, early detection is of
83 utmost importance.

84 The signs and symptoms of patients presenting with intraocular Rb in high-income countries
85 are well documented. Studies from Europe and the United States have been consistent in
86 showing that patients most commonly present with leukocoria (50-60%), strabismus (20-
87 25%), or inflammation (6-10%) (5–8). Presenting signs have been shown to correlate with
88 ocular survival; Abramson *et al.* (9) have reported improved ocular survival in patients
89 presenting with strabismus compared to leukocoria.

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

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

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109 **Patients and Methods**

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

119
120 **Orthoptic Assessment**

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

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133 **Classification of Presenting Signs**

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

143 Data were entered into Excel version 16.0 (Microsoft Corp., Redmond, WA, USA) and SPSS
144 version 22.0 (SPSS Inc., Chicago, IL, USA) was used to analyze all data. Categorical
145 variables were compared with Chi-squared test. The statistical significance level was set at
146 0.05. Data throughout is presented as medians.

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149 **Results**

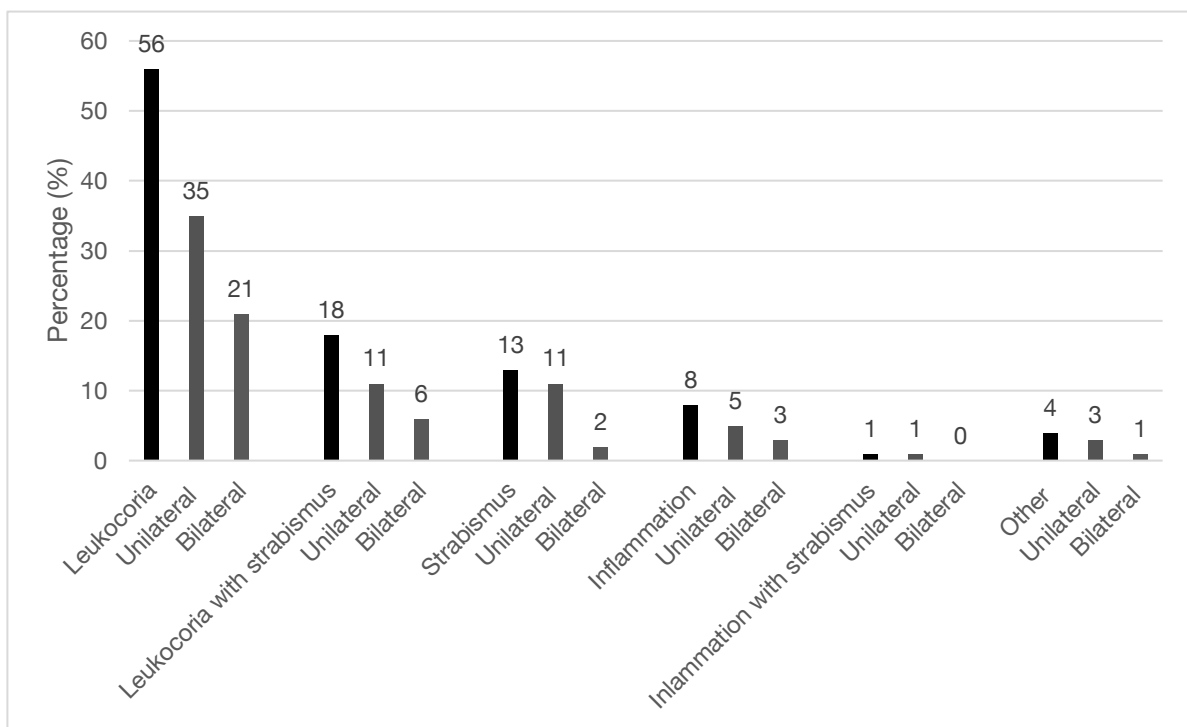
150 **Presenting Features**

151 Of the study cohort, 88 (67%) patients presented with unilateral retinoblastoma, and 43
152 (33%) with bilateral disease (174 eyes in total). The median age at presentation was 16 and

153 10 months respectively. Sex was female in 65 patients (49.6%) and male in 66 patients
 154 (50.4%) (Table 1).

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

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Figure 1. Distribution of Presenting Signs in 131 Rb Patients

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Strabismus

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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.

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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

180 alone, as it was there only presenting sign. Of the 17 patients who presented with strabismus
181 alone, 5 had deviations that were smaller than 15 degrees or ‘moderate’ on orthoptic
182 assessment, and 6 had a variable strabismus.

183 Small angle strabismus was a feature of 33 (25%) presentations in total in this series, with 24,
184 three and one patients in the leukocoria, inflammation, and other groups respectively having a
185 small angle strabismus. Furthermore, eight and six patients in the leukocoria and
186 inflammation groups had a variable strabismus. If *all* strabismus is considered, regardless of
187 the angle of measurement or variability, then 66% of patients presenting with Rb would be
188 classified as having strabismus as a feature of their presentation; 53% of Rb patients would
189 be classified as presenting with leukocoria and strabismus, 21% with leukocoria alone, and
190 13% with strabismus alone.

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

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194 **Foveal involvement**

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

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

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

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

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219 **Ocular Survival**

220 Of 131 presentations, 63% (n=83) underwent enucleation as their primary treatment, which
221 reflects the high proportion of D and E eyes in the cohort (Table 1). 75% of patients who
222 presented with Strabismus were enucleated compared with 51% of patients who presented

223 with leukocoria (P = 0.08). Combining all patients who had Strabismus as a feature of their
 224 presentation (LS and S), 69% underwent primary enucleation; this was not significantly
 225 higher than in patients presenting with leukocoria alone (P = 0.06).

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

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

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

	L				LS				S				I			
	Unilateral		Bilateral		Unilateral		Bilateral		Unilateral		Bilateral		Unilateral		Bilateral	
IIRC Group	Salvage	Enuc	Salvage	Enuc	Salvage	Enuc	Salvage	Enuc	Salvage	Enuc	Salvage	Enuc	Salvage	Enuc	Salvage	Enuc
A	100%															
B									100%					100%		
C	100%		100%						100%							
D	65%	35%	100%		66%	33%	100%		80%	20%	100%					
E		100%	25%	75%	11%	89%		100%		100%	50%	50%		100%		100%
		(20)	(4)	(12)	(1)	(8)		(4)		(8)	(1)	(1)		(7)		(3)

235
 236 **Table 1. Percentage and number (parenthesis) of patients who underwent primary enucleation vs globe-**
 237 **sparing therapy relative to IIRC presenting stage and disease laterality. Enuc: enucleation**

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245 **Discussion**

246 The signs of leukocoria and strabismus may have been falsely dichotomized in previous
247 descriptions of the presenting signs of Retinoblastoma. Major studies that have investigated
248 the presenting signs of Rb vary in the time period over which data was collected; one Finnish
249 study collected data from patients presenting between 1912 and 1964 (5), an English study;
250 1960-1970 (6), and two North American studies; 1960-1969 (7) and 1960-1990 respectively
251 (8). Within each study, patient presentations were categorized according to a single
252 presenting sign. Trincado et al. (18) reported that 2 out of their group of 41 patients sought
253 medical attention due to both leukocoria and strabismus; their cohort did not undergo
254 orthoptic assessments.

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

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

273 It has been shown that exotropia is more common than esotropia in patients presenting with
274 Rb by a factor of 3:1. Strabismus affects 2.1% of the population (20) and is normally
275 expected to occur at a ratio of 3:1 eso- to exo-deviations (17). Previous studies have reported
276 that esotropia was more common than exotropia in patients presenting with Rb (8). Patients
277 with constant exotropia are more likely to have coexisting ocular or systemic disease (21).
278 The findings from our study demonstrate that Rb is consistent with this observation, and
279 clinicians should be vigilant when assessing patients with constant exo-deviations. We have
280 previously assessed the long-term results of strabismus and showed that at presentation 15 of
281 20 patients had an exotropia (13). This larger study confirms the ratio of eso-:exo-deviations
282 in the Rb population at presentation and is relevant to all pediatric ophthalmologists who will
283 be referred such patients.

284 The group of patients presenting with strabismus alone sheds further light on the subtlety of
285 some strabismus presentations in Rb. Five of these 17 patients had small angle strabismus
286 measuring less than 15 diopters, and 6 had variable strabismus, yet strabismus was their only
287 sign at presentation. If all strabismus is considered, regardless of the angle of measurement
288 or variability, then 66% of patients would be classified as having strabismus as a feature of

289 their presentation. Leucocoria with strabismus would be the most common presentation;
290 53% of patients. Strabismus may have been overlooked in patients presenting with
291 leukocoria in previous studies. The reverse is also possible however the authors feel that
292 Strabismus is harder to assess and has been less of a focus of Rb awareness campaigns; it is
293 more likely to have been missed in the past. Strabismus may be best evaluated by a
294 specialized orthoptist. Early detection of Rb in patients presenting with strabismus, in the
295 context of a high probability of foveal involvement, may be globe sparing. Physicians should
296 be alert to small angle deviations, and should be aware that exotropias of infancy are more
297 likely to confer pathology (21), retinoblastoma or otherwise.

298
299 Overall enucleation rates were lower in our data set than previous studies, reflecting changes
300 in diagnosis and treatment of Rb. Previous studies have captured data spanning wide time
301 points during which treatment paradigms have shifted. Enucleation, which was previously
302 the treatment of choice in advanced disease (22), has reduced in frequency since the
303 introduction of systemic, intra-arterial and intra-vitreous chemotherapy. Indeed, even within
304 the time course of this study, the enucleation rate in unilateral group D eyes has fallen
305 significantly due to changes in treatment approach.

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

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

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

331 In conclusion, leukocoria and strabismus can occur at the same time in retinoblastoma.
332 These two signs may have been falsely dichotomized in the past and it is now understood that
333 many patients have a combination of both. We have confirmed that exotropia is more
334 common than esotropia at presentation in the largest cohort that has had an orthoptic
335 assessment. The angle of deviation may be small, and the presence of strabismus in

336 retinoblastoma may be considerably higher if small angle strabismus is considered.
337 Specialist orthoptic assessment is recommended to assess retinoblastoma patients to
338 accurately detect strabismus. We have also shown that foveal involvement is common in
339 patients with Strabismus where early detection may be globe sparing. We believe this is
340 important information for paediatric ophthalmologists and awareness campaigns that attempt
341 to improve early detection.

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352

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