Delayed Diagnosis of Retinoblastoma: Analysis of Degree, Cause, and Potential Consequences

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ABSTRACT. *Objective.* **To assess the degree, cause, and consequence of delays from presenting signs to diagnosis of retinoblastoma.**

Methods. **A retrospective chart review was conducted of 64 consecutive patients who presented to the Memorial Sloan-Kettering Cancer Center with newly diagnosed retinoblastoma. Seven patients with a positive family history were excluded.**

Results. **The median times from presenting signs to diagnosis for patients with unilateral and bilateral disease were 1.5 and 2.25 months (range: 0–46), respectively; for those who presented with leukocoria and strabismus, median times were 1.5 (range: 0–46) and 2.5 months (range: 0–24). Parents noted the first signs in 75% of the cases. Seventy-seven percent delayed seeking treatment, and primary care physicians (PCPs) delayed referral in 30%. Only 3 patients were referred from PCPs solely for physical examination findings. No adverse consequence of delayed diagnosis could be established clearly, but a trend toward eye loss being associated with longer delays in patients with bilateral retinoblastoma was noted.**

Conclusion. **Leukocoria and strabismus secondary to retinoblastoma are usually first recognized by relatives rather than PCPs. At routine visits, PCPs should inform parents about the importance of reporting eye abnormalities, and children whose parents complain of leukocoria (white, shiny, jello-like eye) should be referred promptly to an ophthalmologist regardless of whether an absent red reflex is appreciated.** *Pediatrics* **2002;109(3). URL: http://www.pediatrics.org/cgi/content/full/109/3/e45;** ***retinal neoplasms, newborn infant screening, strabismus, eye enucleation.***

ABBREVIATION. PCP, primary care physician.

Retinoblastoma, the most common primary ocular tumor in children, has an incidence of approximately 1 in 14 000 to 34 000 live births per year.[1] Treatment has improved dramatically during the past 80 years, and currently >90% of children who receive a diagnosis of retinoblastoma in the most developed countries are cured.[2]

Earlier detection of the tumor influences prognosis and in recent years has allowed for more conservative eye-sparing treatment of retinoblastoma.[3–5] Erwenne and Franco[6] found that advanced age and delayed diagnosis increase the chance for extraocular disease that mandates significantly more aggressive treatment. Shields et al[3] found an increase in eye-sparing treatment modalities from 1974 to 1988; they postulated that increased awareness and earlier diagnosis of unilateral disease may result in smaller tumors that can be treated conservatively. Abramson et al[7] found no risk to life by attempting conservative management initially in all groups, although the majority of patients with Reese-Ellsworth groups IV and V eventually underwent enucleation. More important, 34 of the 39 eyes with tumors in Reese-Ellsworth groups I to III were spared with the use of radiation, plaque brachytherapy, cryotherapy, and photocoagulation as alternatives to enucleation.

We noted that a few patients presented to our center with long delays between initial appreciation of signs or symptoms and diagnosis. We therefore decided to perform this retrospective study to try to identify the reasons for delayed diagnoses. We also wanted to clarify the role of the standard red reflex examination performed by many pediatricians in the diagnosis of retinoblastoma.

There is limited literature regarding reasons for delayed diagnosis of retinoblastoma. In the pediatric literature, Abramson et al[8] reviewed at length the presenting signs of retinoblastoma, but delays to diagnosis were not addressed. Haik et al[9] reviewed 250 cases of retinoblastoma for the presenting symptoms and delays to diagnosis, but they published their work in a journal referenced almost exclusively by ophthalmologists. Goddard et al[10] in the United Kingdom reported that nearly half of their patients were referred to an ophthalmologist within 1 week of presenting to a primary care physician (PCP), but another quarter of patients experienced a delayed referral from the PCP of more than 8 weeks. The same article emphasized a need for education of the PCP but was published in an ophthalmologic journal unlikely to be read by PCPs. It is the PCP who can alter treatment options for the patient with prompt referral and diagnosis; therefore, it is imperative that he or she have the appropriate skills for recognition of retinoblastoma.

METHODS

The clinical charts of 64 consecutive patients who presented to the Memorial Sloan-Kettering Cancer Center with newly diagnosed retinoblastoma between November 11, 1993, and January 14, 1998, were reviewed. Seven patients with a family history of retinoblastoma were excluded from the results, and analyses were

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performed on the remaining 57. The patient's history was recorded in a uniform format and obtained in an interview with the parent or primary caregiver. The following clinical parameters were recorded and analyzed: laterality of the disease, age at diagnosis, presenting signs, who first noted the presenting signs, and time from the onset of presenting signs to diagnosis. When any delay was noted, the reasons for the delay and potential consequences of the delay were also recorded. The potential consequences analyzed were choroidal extension, metastatic disease, enucleation versus eye salvage, and survival. The analyses were conducted using both the log-transformed *t* test and the Wilcoxon nonparametric test. Two cases reported a time of "a few months" from onset of signs to time of diagnosis and were coded as an interval of 2.5 months.

RESULTS

Interval From Onset to Diagnosis

The age at diagnosis of the 57 children ranged from 1.5 to 116.3 months. Unilateral disease was present in 41 of 57 of these children (72%). Their median age at diagnosis was 23.3 months, and the median time from initial presenting signs to diagnosis was 1.5 months (range: 0–46 months). Six of the 41 patients (15%) with unilateral disease had no delay from signs to diagnosis. In patients with bilateral disease, the median age at diagnosis was 12.8 months, and the median time from initial presenting signs to diagnosis was 2.25 months (range: 0–24 months). Four of the 16 patients (25%) with bilateral disease had no delay from signs to diagnosis.

The parents first noted the onset of signs in 43 of 57 cases (75%). In 6 cases, relatives first noted them, in 1 case a visiting nurse, and in 1 other a physical therapist. An 8-year-old patient who presented with abrupt loss of vision noted the problem himself. The PCP first noted the presenting sign in 3 of 57 patients (5%). In these 3 cases, the PCP recognized that the patient had an ophthalmologic problem despite lack of an ophthalmologic complaint from the family. These included a 10-month-old who was noted to have strabismus, a neonate with an absent red reflex, and a third patient whose record did not clearly state the abnormality detected. No record of who noted the presenting signs was available in 2 cases.

Leukocoria and strabismus were the most common presenting signs noted in the diagnosis of retinoblastoma (Table 1). Leukocoria—described by parents as something white, shiny, jello-like, or a discoloration of the eye—was reported as a presenting sign in 37 of 57 patients (65%). Their median delay to diagnosis was 1.5 months (range: 0–46 months). Three of the 37 patients (8%) who presented with leukocoria had no delay to diagnosis, and 1 patient received a diagnosis after only 2 days. Strabismus, described by parents as deviation of the eye, a "lazy" eye, crossing of the eyes, or an eye "turned in," was reported as a presenting sign in 15 of 57 patients (26%). Their median delay to diagnosis was 2.5 months (range: 0–24 months). One of the patients with strabismus had no time delay to diagnosis.

Loss of vision was noted in 4 of 57 cases (7%), and less specific complaints including an "abnormality" in the eye, a "dilated" eye, or a "red, itchy eye" were noted in an additional 5 of 57 (9%). The 9 of 57 patients (16%) with less common complaints had a median delay time of 0 months (range: 0–12 months). Five of these 9 patients had no delay to diagnosis, 3 of whom had varying degrees of vision loss.

Reason for Delays

A delay in seeking treatment was defined as the interval from presenting signs noted by the patient, parents, or others to the time at which a physician was notified of those signs. A delay in seeking treatment accounted entirely for the delay to diagnosis in 30 of 47 patients (64%) with delays and for a portion of the delay in another 6 patients (13%). Time delayed in seeking treatment ranged from 0.25 to 11 months (median: 1.5 months). In 43 of 57 cases (75%), the parents reported having seen a PCP before seeing an ophthalmologist. The other 14 patients presented initially to an optometrist, were seen directly by an ophthalmologist, or did not specifically report the PCP's role in the diagnosis.

A delayed referral from the PCP to the ophthalmologist was defined as the interval from the time the physician was notified of the presenting sign to the time a referral was made to an ophthalmologist. Delayed referrals from the PCP to the ophthalmologist accounted entirely for the delay to diagnosis in 10 of 47 patients (21%) with delays and for a portion of the delay in 4 patients (9%). In all of these patients, parents stated that they reported the presenting signs to the child's physician, who reassured the parents of normalcy or made a diagnosis different from retinoblastoma, neither of which initiated an immediate referral to ophthalmology. One of these patients had only a 2-day interval from presenting sign to diagnosis, but the remaining 13 cases had a median delay of 3.75 months (range: 1–46 months). Table 2 outlines the time interval from each presenting sign to diagnosis in these 14 patients. Of note, 1 patient's diagnosis was delayed 4 months because the pediatrician felt comfortable with the patient's lateral deviation of the eye in the presence of a red reflex. None of the other parents involved with delayed referrals were able to clarify the reason that the physician decided that an ophthalmology referral was unnecessary.

TABLE 1. Interval From Presenting Signs to the Diagnosis of Retinoblastoma

Presenting Sign	Interval (Days)*					Median Interval (Months)	Range (Months)
	0	1–14	15–30	31–60	>60		
Leukocoria	3	5	7	4	18	1.5	0–46
Strabismus	1	2	3	0	9	2.5	0–24
Other presenting signs	5	1	1	1	1	0	0–12

* Total number of signs is larger than total number of patients secondary to 2 presenting signs in some patients. One patient with no delay had no reported presenting sign.

TABLE 2. Presenting Signs in Patients With Delayed Referral From the PCP

Presenting Sign	Interval (Days)				Median Interval (Months)	Range
	1–14	15–30	31–60	>60		
Leukocoria	1	0	0	5	5.3	2 d–46 mo
Strabismus	0	0	0	5	4	2.6–24 mo
Other presenting signs	0	1	1	1	2	1–12 mo

Three patients had delays to diagnosis for other reasons. One patient had a 1-month delay because an ophthalmologist originally diagnosed Coats' disease in the patient. Two patients had some time delay between referral from the PCP to an actual appointment with the ophthalmologist. Of these 2 patients, one parent could not get an appointment through the patient's health maintenance organization for 3 weeks. The other patient had a delay of 4 months from the PCP's referral to the ophthalmology appointment. The record is unclear as to why there was such a significant delay to get to the ophthalmologist except to state that the patient was not originally seen in the United States.

Analysis of Potential Adverse Consequences

In patients with bilateral disease, the median time delay to diagnosis for the 15 salvaged eyes (eyes treated with measures other than enucleation) was 0.5 months, and the median delay in the 17 unsalvaged eyes was 2.67 months. Three of our patients were left blind after bilateral enucleation; they had delay times of 2.5, 3, and 24 months. A trend toward longer delays being associated with eye loss in patients with bilateral retinoblastoma was noted but did not reach statistical significance ($P = .17$). Only 2 of the patients with unilateral disease did not have enucleation, and those 2 patients had delays of 0 and 1 month.

The delays to diagnosis in patients with choroidal extension were not significantly different from delays in the patients without aggressive disease at diagnosis. The 3 patients with metastatic disease had delays to diagnosis of 0, 1, and 6 months. All of our patients survived their disease; therefore, patient survival was not affected by the delay to diagnosis.

DISCUSSION

With an incidence of 1 in 14 000 to 34 000, retinoblastoma is not a common problem in general pediatrics. However, its prompt diagnosis can influence treatment and the prognosis of saving the eye.[3] Family members often first recognize the initial signs of retinoblastoma, but in 77% of our patients, these family members unwittingly contributed to their child's delay by not seeking prompt treatment. A brief question added to the PCP's history at the newborn and 2-, 4-, and 6-month visits may educate the parents to alert the physician of eye abnormalities such as leukocoria and strabismus.

Diagnosis of retinoblastoma has been an important diagnostic dilemma for the pediatrician.[9] Five of the 14 patients who encountered a delay to diagnosis after alerting the PCP presented with strabismus, and 6 of these 14 presented with leukocoria. Although recommendations for referral for strabismus in the first few months of life are not very clear, leukocoria is very clearly stated to be a sign for which immediate referral is necessary. Presumably a proportion of these patients were not referred because the signs were not reproducible in the clinic. We believe that a misunderstanding of the significance of a positive red reflex may have hindered prompt referral of these children to ophthalmologists. One of our patients clearly had a delayed referral secondary to the presence of a red reflex. Many more cases of delayed referral could have involved similar reasoning, but it was often unclear why the PCP assured the parents of normalcy. A study that would include not only history obtained from interviewing the parent but also a review of the original chart from the PCP's office may help answer this question.

Small retinoblastomas may produce only perceptible leukocoria when the pupil is dilated, such as in a dark room when a family member goes to check on the child. Small or peripheral retinoblastomas may not produce an easily recognized absent red reflex under conditions normally present in a well-child examination room. Pupil dilation in the pediatrician's office has been discussed as a solution to this problem[11,12]; however, the time constraints of a pediatrician may preclude an accurate and thorough ophthalmologic examination.[13] Small retinoblastomas may not produce leukocoria even when dilated. Therefore, a parent's complaint of any condition resembling leukocoria should be viewed with suspicion and as grounds for referral to an ophthalmologist regardless of the red reflex examination.

A review of pediatric textbooks was performed to determine whether it is clearly stated that although an absent red reflex is a sign of ocular pathology, the converse is not true; the presence of a red reflex does not ensure the absence of ocular pathology. With the exception of 1 textbook,[14] it is clearly stated that leukocoria warrants an ophthalmologic referral, and many pediatric textbooks encourage a thorough ophthalmologic examination by 3 to 4 years of age.[15,16] It is important to note, however, that our median age of diagnosis for children with unilateral disease was 23.3 months, consistent with the median age of 24 months from a study of 1531 patients from 1914 to 1983.[2] In the first few years of life, the funduscopic examination is often limited to assessing the presence of the red reflex. Only 1 of our patients was suspected of having retinoblastoma solely because of an absent red reflex noted on a routine physical examination. One prominent textbook suggests that a red reflex could potentially rule out serious pathology[17] (Table 3). Others discuss the red reflex exami-

TABLE 3. Textbook Recommendations Regarding the Red Reflex Examination

Textbook	Recommendations
Rudolph's Pediatrics, 20th Edition 1996[14,19]	Focusing down to the retina and visualizing retinal vessels will verify a normal retina is being seen. . .A white pupillary reflex is abnormal and may occur with a large retinoblasto ma or developmental abnormalities.[19] . . . Referral of patients with leukocoria to an ophthalmologist is *usually* indicated.[14]
Nelson Textbook of Pediatrics, 15th Edition 1996[15]	Ideally, every child should have a thorough ophthalmologic examination sometime in early childhood, preferably by the age of 3–4 years; these are the crucial years for detect ion and treatment of amblyopia, strabismus, high refractive errors, and many other significant disorders. (A table suggests the red reflex test be performed from the newborn period through the 5-year examination).
Oski's Pediatrics, Third Edition 1999[18]	In the funduscopic examination, use a zero lens and note the presence of a red reflex, or hemorrhages. . .Any obstruction, such as corneal or lenticular cataract, will obliterate part or all of the red reflex.
Nelson Textbook of Pediatrics, 16th Edition 2000[17]	The presence of bilateral red reflexes suggests the absence of cataracts or of intraocular pathology (chapters 629, 634–639). Leukocoria (white pupillary reflex) suggests cataract, tumor. . .and warrants an ophthalmologic consultation.

nation but do not clearly note its limitations.[14–19] The red reflex examination is an appropriate part of the examination in the healthy newborn for lack of a better, noninvasive method, but its limitations must be recognized.

The argument can be made that the low incidence of retinoblastoma does not warrant such concern for the general pediatrician. The New York State newborn screening program, however, tests for phenylketonuria (1/18 000), maple syrup urine disease (1/268 000), galactosemia (1/57 000), and biotinidase deficiency (1/80 000),[20] all diseases that, although rare, have preventable consequences when detected early. Retinoblastoma also has preventable consequences when detected early.[2]

Pediatric ophthalmologists and oncologists have made great strides in the treatment of this disease. A study from Los Angeles Children's Hospital in 1958 noted a mortality rate of 9 of 50 patients (18%) with unilateral retinoblastoma and 11 of 22 patients (50%) with bilateral retinoblastoma.[21] By 1984, the overall mortality had decreased to 9%,[22] and survival has remained at >90% in industrialized countries such as the United States. Earlier detection may allow more widespread use of eye-sparing treatments, minimizing the morbidity of this disease. Although the adverse consequences in our study did not statistically correlate with delay, a trend was noted to suggest that eyes with retinoblastoma, which were able to avoid enucleation, had a decreased time delay to the diagnosis in patients with bilateral disease. The median delay for the salvaged eyes is approximately 20% of the unsalvaged eyes. The lack of statistical significance may be attributable to the limited power of our small sample size. A larger study, especially in this era in which alternative treatments to enucleation are continually becoming more available, might include more patients who did not have enucleation as a treatment for their retinoblastoma, and the trend that we observed might reach statistical significance. It has been shown that smaller tumors diagnosed at an earlier stage of disease are more amenable to alternative treatments, which aim to avoid enucleation and preserve vision.[7] All professionals who are involved in the diagnosis and treatment of retinoblastoma must recognize that the PCP plays a vital role in the detection of retinoblastoma. With increased awareness, improved patient education, and immediate referral for ocular complaints suggestive of leukocoria, more children may have access to eye-sparing treatment modalities and avoid other, less optimal outcomes.

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