ABSTRACT. In the United States, 50% of all retinoblastoma cases are diagnosed after the observation of leukocoria by a family member or primary care physician. However, leukocoria produced by retinoblastoma lesions can often be missed by direct ophthalmoscopic examination through an undilated pupil. The purpose of this study is to demonstrate the utility of pupillary dilation for the detection of leukocoria in suspected cases. Seven patients (10 eyes), aged 2 days to 20 months, with retinoblastoma were examined for leukocoria using a direct ophthalmoscope with the pupils first undilated and then after pharmacologic dilation with 0.5% cyclopentolate and 2.5% phenylephrine. Leukocoria was detected by direct ophthalmoscopy on undilated examination in 3 of 10 eyes (30%). In contrast, leukocoria was observed after pupillary dilation in 10 of 10 eyes (100%). The retinoblastoma lesions, from 2 to 10 mm in diameter, were located within the posterior 45° of the retina. Pupillary dilation is a safe and effective tool that can enhance the ability of the examiner to detect leukocoria. Dilation may afford early diagnosis and treatment, and therefore should be considered on patients in whom the diagnosis of retinoblastoma is entertained. Pediatrics 1999;104(4). URL: http://www.pediatrics.org/cgi/content/full/104/4/e44; direct ophthalmoscope, leukocoria, pupillary dilation, retinoblastoma.

Retinoblastoma, the most common intraocular malignancy of childhood, occurs in 1 of 20 000 live births with 200 to 300 new cases reported in the United States per year, and has no sexual or racial predisposition.1 Caused by a mutation in the retinoblastoma gene, which is located in the long arm of chromosome 13 (13q14), ~94% of newly diagnosed retinoblastoma cases are sporadic whereas only 6% are inherited as a familial tumor.2–4 With a mean age at diagnosis of 12 months for inherited and 18 months for sporadic cases, retinoblastoma can involve 1 or both eyes, with one third of all cases having bilateral involvement.5 The survival rate for patients with retinoblastoma is 92%.6 With such a high survival rate, the incidence of retinoblastoma has increased, and the likelihood of seeing children with retinoblastoma is accordingly increased.

The goal of treatment is to save life and, if possible, vision. Treatment depends on the clinical presentation. Factors such as bilaterality, size, location, and number of retinoblastoma tumors influence which treatment modality is selected. A delay in diagnosis can result in large and/or multiple tumors, which reduces the possibility of preserving life and vision. In these cases, enucleation may be the only treatment option. On the other hand, early diagnosis permits local treatment because the tumors are small. Local treatment for retinoblastoma such as laser photocoagulation, cryopexy, or episcleral plaque radiotherapy, is minimally invasive with low morbidity and high treatment success in which both life and vision are maintained.7–9 Recently, combination therapy using chemotherapy with local treatment modalities has been advocated to salvage vision in advanced cases.10,11

The most common presenting sign in retinoblastoma is leukocoria (white pupillary reflex), which occurs in 50% to 62% of cases.12 In a normal eye, if light is directed into the pupil, the pupillary space will appear as a homogeneous bright reddish-orange color that is called the red reflex. It is a reflection of the choroidal vasculature and retinal pigmentation.13 Retinoblastoma, which appears as a white mass overlying or infiltrating the retina, interrupts the red reflex when light is shined in the eye. The red reflex is best seen by looking into the pupil with a direct ophthalmoscope. However, it can be difficult to visualize through a small pupil.

Pediatricians and other primary care physicians usually have the first opportunity to evaluate a child suspected of having leukocoria. However, the infant pupillary examination can be difficult and the detection of leukocoria can be missed despite the presence of a retinoblastoma lesion, especially in a small pupil. Pharmacologic pupillary dilation can enhance the examiner’s ability to detect both the red reflex and leukocoria. The purpose of this study is to demonstrate that the detection of leukocoria using direct ophthalmoscopy is enhanced with pupillary dilation.

METHODS

Seven consecutive patients in whom the diagnosis of retinoblastoma was confirmed by ophthalmologic examination, ultrasonography, and radiologic imaging were examined for the presence of leukocoria by one ophthalmologist (J.T.H.) with a direct ophthalmoscope under two conditions. At the time of pupillary examination, the examiner was masked to the eye and location of tumors. The patient was held in the lap of the parent to obtain maximum cooperation. The pupil was visualized through the ocular of a direct ophthalmoscope that was held at arm’s length. With the patient in primary gaze, the pupillary reflex was examined directly in front of, and at several different angles to assess the superior, nasal, inferior, and temporal quadrants of the retina.

From the Department of Ophthalmology, University of California, Davis, Sacramento, California.

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Reprint requests to (J.T.H.) Department of Ophthalmology, UC Davis Medical Center, 4860 Y St, Suite 2400, Sacramento, CA 95817. E-mail: jthanda@ucdavis.edu

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Leukocoria was defined as an observed reduction in the red reflex. Testing for leukocoria was performed first under typical medical office lighting conditions that maintains the pupils constricted, before pupillary dilation. The pupillary diameter was measured after 3 seconds of illumination on the pupil, and the presence or absence of leukocoria was recorded. The pupils were pharmacologically dilated with 1 drop to each eye twice of 0.5% cyclopentolate and 2.5% phenylephrine. Approximately 30 minutes later, the pupillary diameter was measured, and the pupillary examination with a direct ophthalmoscope was repeated with the examination room lights off. Each pupillary examination lasted ~30 seconds. Retinoblastoma tumors were confirmed using indirect ophthalmoscopy and detailed retinal drawings of the lesions were made. Ultrasonography and fundus photography were performed during an examination under anesthesia to further characterize the extent of disease.

RESULTS

Seven consecutive patients (4 boys and 3 girls) aged 2 days to 20 months (10 eyes) with suspected, and later confirmed, retinoblastoma were included in the study. Four of these patients had bilateral disease of which 1 patient had an enucleation before inclusion in the study. The average undilated pupillary diameter in a fully illuminated room was 3 mm. Leukocoria was detected in 3 of 10 eyes (30%) with retinoblastoma under these conditions. In the remaining 7 eyes, a red reflex was seen in 1 and an indeterminate reflex (neither leukocoria nor a red reflex) was seen in 6 eyes. After pupillary dilation, the average pupillary diameter was 7 mm. Leukocoria was observed with direct ophthalmoscopic examination of pupils in all 10 eyes (100%; Fig 1).

The size of the lesions identified by indirect ophthalmoscopy ranged from 2 to 10 mm in diameter and they were confined to the posterior pole (posterior 45°). Figure 2 shows a composite retinal map illustrating the sizes and locations of the retinoblastoma tumors that elicited leukocoria only after dilated, direct ophthalmoscopic examination. The 3 eyes that demonstrated leukocoria before pupillary dilation had either large tumors (patient 3, left eye, and patient 4, left eye) or a moderately sized tumor in the macula (patient 7, left eye). The case histories of the 7 patients are summarized in Table 1.

DISCUSSION

In this series of 7 patients (10 eyes) with confirmed retinoblastoma tumors, which ranged from 2 to 10 mm in diameter, undilated direct ophthalmoscopic examination elicited leukocoria in only 3 eyes although it became observable in all eyes after pharmacologic pupillary dilation. Pupillary dilation enabled us to observe leukocoria from small retinoblastoma tumors in the posterior pole, moderately sized lesions located outside of the macula, and a moderately sized posterior lesion in an uncooperative patient. The results of this study perhaps reflect the maximal improvement in the ability to detect leukocoria because the examiner was an ophthalmologist, and the patients were referred for the suspicion of retinoblastoma. Although we did not determine the effectiveness of this technique for the primary care physician, we believe with practice, the primary care physician can become proficient with the pupillary examination just as he or she uses the otoscope to diagnose otitis media.

The size of the pupil has a dramatic impact on the area of retina evaluated during the direct ophthalmoscopic examination. The amount of light that passes through the pupil, reflects off the retina, and exits back through the pupil, depends on the pupillary size. In a small pupil, the retinal area examined for leukocoria is confined to the macula because it is aligned with the pupillary axis. With a small pupil, only tumors that have grown large enough to interrupt the pupillary axis may be detected as leukocoria. In the undilated state, we observed leukocoria in patient 3 (left eye) and patient 4 (left eye) because these tumors were large and had crossed into the pupillary space. We believe that leukocoria was detected in the undilated pupil of the left eye in patient 7, not only because of its size, but also in part, because of the tumor’s macular location. Furthermore, in the 7 eyes without obvious leukocoria, we confirmed a red reflex in only 1 eye, which suggests that a small pupil can prevent the observer from obtaining a quality pupillary examination.

Pupillary dilation improved our ability to observe leukocoria resulting from small retinoblastoma lesions in the posterior pole and larger lesions located outside of the posterior pole. Leukocoria was detected after pupillary dilation in a posteriorly located, isolated tumor as small as 3 mm (patient 3). Likewise, tumors ranging from 2 to 5 mm in diameter adjacent to the optic nerve (patients 1, 2, 6, and 7) were detected after the pupils were dilated. We believe that our ability to find leukocoria in these patients was enhanced in part, because the combined size of the optic nerve and retinoblastoma lesions enlarged the area that blunted the red reflex. Pupillary dilation also improved our ability to observe lesions located outside of the macula. Patients 3 (right eye) and 4 (right eye) had moderately sized tumors located in the nasal retina. A large pupil allowed us to examine peripheral areas of the posterior pole.

Patient 5 presented with a moderately large tumor in the posterior pole that was missed during the undilated pupillary examination, but was seen after the pupil was dilated. This child, who suffers from developmental delay, was very uncooperative. As a result, the pupillary examination was difficult. Pupillary dilation may be especially useful in situations when patient cooperation is suboptimal, and efficient testing for leukocoria is essential.

Pupillary dilation can be incorporated into the general pediatric examination by instilling dilating drops at the beginning of the appointment. The pupillary examination takes 30 seconds to perform, and thus, is not time consuming. Because pupillary dilation takes 20 to 30 minutes, the leukocoria check can be performed either at the conclusion of the general examination or if the pupils are not dilated, after examining another patient at a later time. This technique has been used routinely to screen all new patients within the first 6 weeks of life by the Department of Pediatrics, University of Southern California, and several large pediatric practices in Los Angeles (personal communication, Robert Adler, MD, Associate Chair, Department of Pediatrics, Uni-
Fig 1. A, Direct ophthalmoscopic examination of the right eye of patient 7 during an examination under anesthesia. External photograph demonstrating no leukocoria with undilated pupils. B, External photograph demonstrating leukocoria after pupillary dilation. Note that the leukocoria fills the pupil incompletely because of the small size of the lesion. C, Fundus photograph documenting a 2-mm flat, retinoblastoma tumor just superior to the optic nerve. Note: the lid speculum was used for photographic purposes during the examination under anesthesia, and is not necessary for the pupillary examination in the awake patient.
Patients to consider for dilated pupillary examination include those at risk for retinoblastoma, or patients in whom an abnormal pupillary reflex even if intermittent, was noted by a family member or caregiver. Besides retinoblastoma, leukocoria heralds a significant retinal problem such as astrocytic hamartoma, Coats’ disease, ocular toxocariasis, retinal detachment, retinopathy of prematurity, and vitreous hemorrhage.

Pupillary dilation can be safely and effectively used in the pediatric population. Adverse effects have been observed in children who have received phenylephrine and cyclopentolate such as fever, flushing of the face, tachycardia, hypertension, nausea, and vomiting, but the incidence is low. To minimize side effects, a combination eyedrop such as Cyclomydrl (Alcon Laboratories, Inc, Ft Worth, TX), which contains 0.2% cyclopentolate and 1% phenylephrine, could be considered because of its low concentrations. Many physicians express concern that pharmacologic pupillary dilation will precipitate acute angle-closure glaucoma. This occurrence is rare in children. We believe that the benefit of making an early diagnosis of leukocoria with pupillary dilation far outweighs the risks associated with pupillary dilation.

This study suggests that pupillary dilation can safely and effectively enhance the examiner’s ability to detect leukocoria. Dilated direct ophthalmoscopic examination can detect retinoblastoma tumors that are small and in locations that otherwise would be missed until they grow to a more advanced stage. Prompt early referral to an ophthalmologist from early diagnosis could save life and sight.

<table>
<thead>
<tr>
<th>Patient No., Age, and Sex</th>
<th>Eye</th>
<th>Leukocoria</th>
<th>Tumor Size</th>
<th>Tumor Location</th>
<th>Treatment and Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1* 4 mo female</td>
<td>Left</td>
<td>No</td>
<td>Yes</td>
<td>3.5 mm</td>
<td>Peripapillary</td>
</tr>
<tr>
<td>2 5 mo male</td>
<td>Right</td>
<td>Indeterminate</td>
<td>Yes</td>
<td>2 mm</td>
<td>Peripapillary</td>
</tr>
<tr>
<td>3 6 mo male</td>
<td>Right</td>
<td>Indeterminate</td>
<td>Yes</td>
<td>2 mm</td>
<td>Nasal quadrant</td>
</tr>
<tr>
<td>4 6 mo male</td>
<td>Right</td>
<td>Indeterminate</td>
<td>Yes</td>
<td>5 mm</td>
<td>Nasal quadrant</td>
</tr>
<tr>
<td>5 20 mo male</td>
<td>Left</td>
<td>Yes</td>
<td>Yes</td>
<td>10 mm</td>
<td>Posterior pole, superior quad</td>
</tr>
<tr>
<td>6 20 mo female</td>
<td>Left</td>
<td>Indeterminate</td>
<td>Yes</td>
<td>5 mm</td>
<td>Peripapillary</td>
</tr>
<tr>
<td>7 2 d female</td>
<td>Right</td>
<td>Indeterminate</td>
<td>Yes</td>
<td>2 mm</td>
<td>Peripapillary</td>
</tr>
</tbody>
</table>

*Patient 1 had the right eye enucleated prior to her presentation at University of California Davis.
size however, that a normal pupillary examination after dilation in a patient whose parent had seen a suspicious pupil does not rule out retinoblastoma or other retinal pathology. Therefore, referral to an ophthalmologist should be strongly considered. Finally, this technique may stimulate heightened awareness among pediatricians and other primary care physicians of this important clinical sign. We advocate pupillary dilation to become a routine tool in the armamentarium of pediatricians and primary care physicians confronted with the possible diagnosis of leukocoria.

ACKNOWLEDGMENT

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Utility of Pupillary Dilation for Detecting Leukocoria in Patients With Retinoblastoma

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