Abnormal Red Reflex: Etiologies in a Pediatric Ophthalmology Population

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Abstract
Children who present with an abnormal red reflex (ARR) are often referred to ophthalmology due to concern for retinoblastoma. However, an ARR can indicate a wide variety of pathologies, all of which have the potential to develop amblyopia and irreversible vision loss. In this retrospective cohort study, we demonstrate that children who presented with an ARR had a mean age of 22.0 ± 32.5 months and were more frequently referred by their pediatricians (74.5%). The majority of these patients (61.8%) had a normal examination on further evaluation, followed by refractive error (20.4%). Amblyopia was diagnosed in 83.9% of patients with refractive error, with a mean age of 50.3 ± 49.2 months. Because many ARR-associated pathologies require time-sensitive treatment to prevent vision loss, proper screening is critical for diagnosis. Pediatricians play a key role in screening, so education on more common ARR pathologies can better facilitate referrals and improve outcomes.

Keywords
abnormal red reflex, leukocoria, screening

Introduction
Eliciting the red reflex is a useful clinical test used by pediatricians and primary care physicians to screen for ophthalmic conditions in the pediatric population. An abnormal red reflex (ARR) can indicate the need for urgent ophthalmologic referral. One of the most serious conditions causing an ARR is retinoblastoma (RB), which is the most common intraocular malignancy in children1 and a primary concern of many pediatric referrals when an ARR is detected.

An ARR, however, can also be suggestive of other serious, visually significant ocular conditions such as strabismus, Coats’ disease, ocular toxocariasis, persistent hyperplastic primary vitreous, and cataract.2,3 In fact, the most common referrals from pediatricians are for strabismus and refractive errors,4 such as anisometropia, a condition in which the 2 eyes have unequal refractive power, or bilateral astigmatism. Anisometropia, can be further classified as hyperopic (asymmetric far-sightedness), myopic (asymmetric near-sightedness), astigmatic (asymmetric curvature), or mixed.5 All of these conditions, without proper intervention, have the potential to create amblyopia, a vision development disorder commonly known as “lazy eye” in which the eye fails to achieve normal visual acuity.4 Amblyopia can occur due to any ocular condition that limits visual stimulation to the eye so if amblyopia is not treated early, vision loss can be irreversible.

While the differential diagnosis of an ARR has been well described in the literature, no studies to our knowledge have quantified the different types of ocular pathologies found in children who are referred for an eye examination due to an ARR. Since early detection and prompt referral to an ophthalmologist can improve vision outcomes in many of these pathologies, the purpose of our study is to (1) identify the number and mean age of patients who present to a tertiary pediatric ophthalmology practice with an ARR over a 5-year period, (2) quantify and characterize the different types of pathologies found in this population, (3) determine how many patients developed amblyopia secondary to their initial diagnosis and at what age, and (4) provide education on

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common ocular conditions associated with an ARR and emphasize the importance of timely referrals.

**Methods**

This study was approved by the Texas Children’s Hospital Institutional Review Board and adhered to the tenets of the Declaration of Helsinki. A retrospective search of the electronic medical record was conducted for new patients with a chief complaint of “abnormal red reflex” or “leukocoria” seen between March 1, 2013, and March 31, 2018, in a tertiary care pediatric ophthalmology clinic. A total of 173 patients were identified, but 21 patients were excluded due to inaccurate coding.

The following data were collected from the medical record: patient birth date, race, contact date, chief complaint, referral source, lateralization of ARR, detection of ARR in a photograph, visual acuity, cycloplegic refraction, prescription, amblyopia, and final diagnosis. Age of diagnosis (in months) was calculated by subtracting patient birth date from contact date and dividing the total by 365 and multiplying by 12. Detection of ARR in a photograph was determined via the history of present illness and whether the family reported this finding. Prescription was noted if glasses were necessary. Presence of amblyopia was determined based on the initial encounter note, subsequent follow-up notes, or reported examination findings by the pediatric ophthalmologist.

For analysis purposes, patients were categorized as either a normal examination or a confirmed abnormal examination on evaluation by the pediatric ophthalmologist. If they had an abnormal examination, they were grouped into one of the following based on their final diagnosis code: cataract, corneal condition, iris condition, refractive error requiring prescription, retinal condition, RB, or strabismus. Specific details about cataract type and lateralization, type of corneal, iris, and retinal condition, type of refractive error (anisometropia or bilateral astigmatism), type of anisometropia (myopia, hyperopia, unilateral astigmatism, or mixed), lateralization of RB, and type of strabismus (esotropia or exotropia) were also noted.

Statistical analysis was performed with SAS software version 9.4. Correlations between examination findings and race, lateralization of ARR, and detection of ARR in a photograph were determined using the Fisher exact test for categorical variables. For nonnormally distributed variables, groups were compared using the Mann-Whitney-Wilcoxon 2-sample nonparametric test.

**Results**

A total of 152 patients who presented with an ARR were included. The mean age at presentation of these patients to the ophthalmologist was 22.0 ± 32.5 months. The majority of the patients (61.8%; 94/152) had a normal examination, and the most common ocular pathology was a refractive error requiring correction with glasses (20.4%; 31/152). Remaining ocular pathologies diagnosed are represented in Figure 1. Referral source for an ARR was only available for 98% (149/152) of the patients. Children were most often referred by their pediatricians (74.5%, 111/149),
followed by parents who saw an ARR in a photograph (22.8%, 34/149) and other (2.7%, 4/149). Patients who presented due to an ARR seen in a photograph (24.3%, 37/152) did not have an increased risk of having an abnormal examination \((P = .56)\).

An abnormal examination was confirmed in 38.2% (58/152) of the patients. Lateralization of ARR in patients with an abnormal examination was only available for 55 patients, of which 46 patients (83.6%) presented with a unilateral ARR compared with 9 (16.4%) with a bilateral ARR \((P = .002)\). The mean age of patients with an abnormal examination \((33.2 \pm 42.7 \text{ months})\) was greater than that of patients with a normal examination \((15.0 \pm 21.6 \text{ months}, P = .011)\). Similarly, the mean age of patients with amblyopia \((32.9 \pm 44.1 \text{ months})\) was greater than that of patients without amblyopia \((17.6 \pm 25.6 \text{ months}, P = .042)\). A summary of the mean age of diagnosis for amblyopia by final diagnoses can be found in Table 1.

Of the 31 patients with refractive error requiring prescription, 27 (87.1%) had anisometropia and 4 (12.9%) had bilateral astigmatism. Of the 27 patients with anisometropia, 12 (44.4%) had hyperopic anisometropia, 7 (25.9%) had mixed etiology, 5 (18.5%) had astigmatic anisometropia, and 3 (11.1%) had myopic anisometropia (Figure 2). Amblyopia was diagnosed in 26 (83.9%) of the 31 patients with refractive error requiring prescription and 10 (83.3%) of the 12 patients with unilateral cataract.

Of the 12 patients with unilateral cataract, 8 patients had visually significant cataracts that required surgical intervention and subsequent treatment for amblyopia. The mean age at the time of surgery was 17.3 \pm 20.7 weeks. Of the 4 patients who did not require surgery, 2 patients required patching therapy for amblyopia, and 2 had cataracts that were felt to be nonvision threatening and are being followed.

### Table 1. Mean Age of Final Diagnoses in Patients With and Without Amblyopia.

<table>
<thead>
<tr>
<th>Abnormal Red Reflex and Final Diagnoses, (N = 152)</th>
<th>(N) (%)</th>
<th>Mean Age (Months)</th>
<th>(N) (%)</th>
<th>Mean Age (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Amblyopia</td>
<td></td>
<td></td>
<td>Amblyopia</td>
<td></td>
</tr>
<tr>
<td>Normal examination</td>
<td>93 (61.2)</td>
<td>15.1 (\pm) 21.7</td>
<td>1 (0.7)</td>
<td>10.4</td>
</tr>
<tr>
<td>Refractive error</td>
<td>5 (3.3)</td>
<td>34.9 (\pm) 31.1</td>
<td>26 (17.1)</td>
<td>50.3 (\pm) 49.2</td>
</tr>
<tr>
<td>Cataract</td>
<td>2 (1.3)</td>
<td>0.5 (\pm) 0.2</td>
<td>10 (6.6)</td>
<td>6.3 (\pm) 9.5</td>
</tr>
<tr>
<td>Corneal condition</td>
<td>2 (1.3)</td>
<td>31.5 (\pm) 26.9</td>
<td>3 (2.0)</td>
<td>6.7 (\pm) 10.7</td>
</tr>
<tr>
<td>Strabismus</td>
<td>3 (2.0)</td>
<td>59.0 (\pm) 75.2</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Retinal condition</td>
<td>1 (0.7)</td>
<td>69.7</td>
<td>2 (1.3)</td>
<td>6.9 (\pm) 5.3</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>2 (1.3)</td>
<td>17.7 (\pm) 19.9</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Iris condition</td>
<td>1 (0.7)</td>
<td>0.2</td>
<td>1 (0.7)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

![Figure 2. Most patients with a refractive error requiring prescription had hyperopic anisometropia.](image)
Discussion

Given the significant implications of RB and the efficacy of early treatment, RB should remain a chief concern for patients who present with an ARR, especially leukocoria. However, our data show that RB is a relatively uncommon diagnosis in patients who present with ARR when compared with other diagnoses. This is consistent with prior studies that cite the incidence of RB to be between 0.005% and 0.06%. Since detecting an ARR in patients with RB can be difficult, with sensitivity estimates ranging from 16% for peripheral lesions viewed directly to 96% for large lesions viewed obliquely, prompt referral to an ophthalmologist remains critical if leukocoria is a concern to exclude RB as well as other vision-threatening pathologies.

Leukocoria is often noticed by parents or relatives on flash photography, but previous literature suggests that this finding is not a useful predictor of pathology and cannot be reliably used for red reflex screening. With the advent of new technologies, however, improved methodology in smartphone-based applications and artificial intelligence can enhance the detection of RB. Many smartphone applications, such as MDEyeCare and CRADLE for RB screening, Peek Acuity for visual acuity screening, and GoCheckKids for amblyopia screening in children aged 1 to 6 years, have shown great promise in helping primary care physicians make more informed referrals. While these applications still require further development to improve sensitivity across all pediatric age groups, they have the potential to become useful screening tools for common pediatric ocular conditions. According to Google AI research group, artificial intelligence can improve physicians’ diagnostic accuracy; with improvement of traditional red reflex screening through augmented data-driven algorithms, more timely interventions and better outcomes for serious ocular pathologies will be available.

Although pediatricians and families are often worried about RB, we found that visually significant refractive error was the most common cause of an ARR in our study, with the majority of patients having concomitant amblyopia. Patients in our study who had amblyopia presented at an older age than the average age reported in the literature (32.9 months vs 14.4 months), but this may be attributed to the fact that most of our patients had anisometropic amblyopia, which is more frequently asymptomatic and thus more difficult to detect in children <3 years old. Because amblyopia has often developed by the time most children undergo traditional vision screening at 4 years of age, early red reflex testing and new vision screening technologies may allow children with amblyogenic refractive error to be identified prior to the development of amblyopia. In fact, the American Association of Pediatric Ophthalmology and Strabismus recommends instrument-based vision screening for all children beginning at 12 months of age. Pediatricians should note that because amblyopia is commonly regarded as significantly less responsive to treatment after 7 or 8 years of age, evaluations by an ophthalmologist are strongly encouraged if there is any clinical suspicion for anisometropia or a significant refractive error. Because the severity of amblyopia progresses with age and amblyopia occurs during a sensitive period of vision development, early detection of amblyogenic refractive errors via instrument-based screening will allow ophthalmologists the opportunity to initiate appropriate treatment and prevent irreversible visual impairment in a cost-effective manner.

Pediatric cataracts can also lead to the development of amblyopia and cause significant impact on the neurobiological development of a child. Unilateral cataracts, the only type detected in our study, carry a less favorable prognosis than bilateral cataracts, as even a small lenticular opacity can cause significant deprivation amblyopia. In patients with congenital cataracts, unilateral cataract surgery should typically occur around 4 to 6 weeks of age and bilateral cataract surgery by 3 months of age. If the cataract is not deemed visually significant, children can be treated with close observation, patching, and sometimes glasses. Children with later onset cataracts should be managed based on the visual significance of the cataracts. While the mean age of cataract surgery that we reported in our study was older than the age recommended, this may be due to the presence of an acquired cataract, delayed onset of presentation, or delayed referral to an ophthalmologist. When a cataract is suspected in a pediatric patient, the patient should be referred to an ophthalmologist in a timely fashion.

With the possibility of blindness or even death in certain ARR-associated pathologies, pediatricians should always err on the side of caution when referring patients for any abnormalities detected on red reflex testing. Based on the current American Academy of Pediatrics guidelines, all infants and children with a positive family history of RB, cataracts, glaucoma, or retinal abnormalities should be referred to an ophthalmologist regardless of the status of the red reflex test. Given that an improper red reflex test can lead to false positives or diagnostic delays, pediatricians should ensure that appropriate techniques are used in routine examinations and that the child is looking directly at the examiner during the test. Improper techniques can inadvertently display the reflex as falsely dark, off-center, or even white from reflection off of the optic nerve. If a black reflex is noted, which is suggestive of a cataract, corneal scar, or intraocular hemorrhage, then a dilated eye examination or referral to an ophthalmologist should be considered.
Limitations in our study include the dependency on patients to make follow-up appointments to detect subsequent amblyopia development/treatment and variability in final diagnosis coding among providers. This may have limited our ability to identify patients presenting with an ARR to our facility. Additionally, while we entertain the potential of smart-phone applications or artificial intelligence to aid providers in ARR screening, further research is needed to evaluate its role in detecting common pathologies such as those noted in our study.

Conclusion

RB is the most concerning finding in patients who present with an ARR, but pediatricians should be made aware that other visually significant etiologies are more frequently diagnosed. Although the rate of normal ophthalmic examinations is high in these patients, pediatricians should continue to refer patients with an ARR conservatively as treatments for many ARR-associated pathologies are time-sensitive and require early intervention to prevent amblyopia or other causes of irreversible vision loss. Patient education on common causes of an ARR can also encourage engagement and compliance with treatment and follow-up. With improved characterization of ARR diagnoses and the development of new technologies, we hope that pediatricians will be better able to manage and refer patients in their clinical practices with confidence.

Author Contributions

All authors had full access to the data presented and a role in writing the manuscript.

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