The Red Reflex Test and Leukocoria in Childhood

O Teste do Reflexo Vermelho do Olho e a Leucocória na Criança

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Acta Med Port (In Press) • https://doi.org/10.20344/amp.21367

ABSTRACT

The red reflex test, performed using a direct ophthalmoscope, serves as a critical diagnostic tool in identifying various ocular conditions. These conditions encompass retinal anomalies (such as retinoblastoma, Coats disease, retinopathy of prematurity, familial exudative vitreoretinopathy, myelinated nerve fibers, ocular toxocariasis, ocular toxoplasmosis, retinochoroidal coloboma, astrocytic, and combined hamartoma), vitreous abnormalities (including persistent fetal vasculature), lens issues (like cataract), anterior chamber and corneal conditions (comprising dysgenesis of the anterior segment, congenital glaucoma, birth trauma), and tear film disturbances. During this examination, the presence of leukocoria, characterized by a white pupillary reflex, can suggest the presence of underlying conditions. Any suspicion of an abnormal red reflex test warrants immediate evaluation by a qualified ophthalmologist. This article primarily underscores the paramount importance of the red reflex examination, not only to identify potential sight-threatening but also life-threatening conditions. It delves into the most common causes of leukocoria in childhood and offers insights into a comprehensive diagnostic approach. The target audience for this article includes pediatricians, primary care clinicians, and ophthalmologists, all of whom play a pivotal role in the early detection and intervention of these critical eye disorders.

Keywords: Child; Pupil Disorders/diagnosis; Reflex, Pupillary; Retinoblastoma/diagnosis

INTRODUCTION

The red reflex is a fascinating optical phenomenon occurring when light traverses the pupil, reflects off the retina, and then returns through the pupil, manifesting as a reddish-orange glow. This coloration aligns with the natural hue of healthy choroidal vasculature, as all the optical structures within a normal eye, such as the tear film, cornea, lens, and vitreous are transparent. This remarkable occurrence can even be unintentionally observed in everyday life, often appearing in flash photographs.

Abnormal findings in the red reflex, such as dark spots, a weakened reflex, a white reflex, or asymmetry between the reflexes, often indicate irregularities in the transparency of the ocular structures or changes in the coloration of the retina or choroid. It is worth noting that changes in the reflex may be intermittent and contingent on gaze direction, particularly if induced by a localized retinal lesion, often located in the peripheral fundus.

Conducting the red reflex examination, also known as the Bruckner test, entails a semi-darkened room where the ophthalmoscope’s light is projected onto the patient’s eyes from approximately 50 cm away. The direct ophthalmoscope should be set to a lens power of zero and held near the observer’s eyes. Dimming the room lights, if applicable, can facilitate the examination by enlarging the pupillary diameter.

The American Academy of Pediatrics currently advocates that pediatricians or primary care clinicians proficient in this technique perform a red reflex examination on all neonates, infants, and children. This evaluation should occur before discharge from the neonatal nursery and be repeated during routine health supervision visits.
The term ‘leukocoria’ is derived from the Greek words ‘leukos’ (white) and ‘kore’ (pupil) and describes the clinical observation of a white pupillary reflex. Leukocoria is a paramount indicator of retinoblastoma, the most prevalent malignant intraocular tumor in childhood. This seemingly innocuous white pupil reflex is, in fact, a critical red flag that demands immediate attention.

This article’s main objective is to underscore the importance of the red reflex examination in identifying potential vision-impairing and even life-threatening ailments. Furthermore, it elucidates the most common causes of leukocoria and other changes of the red reflex in childhood and offers insights into diagnostic approaches. The intended audience comprises pediatricians, primary care clinicians, and ophthalmologists.

Abnormal red reflex test

Any modification that alters the transparency of the optical medium or changes the natural coloration of the retina or choroid can lead to an abnormal outcome in the red reflex test. These causative factors may be categorized anatomically, ranging from posterior to anterior ocular structures (Table 1).

Retinal causes

Retinoblastoma (RB), the most prevalent malignant intraocular tumor in childhood, stems from mutations in the retinoblastoma gene (RB1) located on chromosome 13q14.2. This condition arises due to the inactivation of both alleles of the RB tumor suppressor gene, resulting in a malfunctioning protein that disrupts the cell cycle and triggers uncontrolled cell proliferation. Inheritance patterns include autosomal dominant transmission in 30% to 40% of instances (hereditary RB), while the remaining 60% to 70% are categorized as sporadic cases without a familial inheritance pattern (non-hereditary RB). Typically, diagnosis occurs before the age of five, with the majority presenting before the age of three, although neonatal diagnosis is less common. Leukocoria manifests as the initial sign in 60% of cases, while strabismus, often associated with a macular lesion, ranks as the second most common early indicator of RB (Fig. 1A).

It is important to note that even unilateral disease does not exclude the presence of a germline mutation, underscoring the need for genetic testing in all RB cases to guide future tumor surveillance. Moreover, RB can exhibit an additional, more complex facet. It may manifest not only in both eyes but also as an intracranial midline primitive neuroectodermal tumor, which is most commonly found within the pineal gland. This unique presentation is referred to as trilateral RB.

In severe cases, this tumor can lead to death if metastasis occurs, typically via the optic nerve. Additionally, the risk of second primary tumors, with osteogenic sarcoma being the most prevalent, further complicates the prognosis.

Early detection and treatment, overseen by a multidisciplinary specialty team, offer the best chance for survival and preservation of ocular function and vision while minimizing the adverse effects of treatment. The standard practice now includes testing for mutations in the RB1 gene, accompanied by screening and genetic counseling recommendations for affected families.

Coats disease is a retinal vascular disorder characterized by retinal telangiectasia, accompanied by intraretinal and/or subretinal exudation, with all occurring without significant retinal traction (Fig. 1B). This condition is typically sporadic and non-hereditary, without associated systemic abnormalities or racial predilection. It most commonly unfolds unilaterally in young males, with diagnoses predominantly occurring during the initial two decades of life. Therefore, it has a later onset compared to RB patients.

Patients with Coats disease may present with visual loss, strabismus, xanthocoria (manifesting as a yellowish reflex), or nystagmus. Notably, the red reflex observed in this condition often exhibits a distinctive yellowish tinge, attributable to the presence of subretinal lipids.

While Coats disease typically presents in childhood and adolescence, it is worth noting that, although rare, cases have been documented in the neonatal period.

Retinochoroidal coloboma is a congenital ocular anomaly of the intricate process of eye formation. It begins with the development of the optic vesicle, an outgrowth from the forebrain. This vesicle subsequently undergoes invagination, giving rise to the double-layered optic cup. The inner layer of the optic cup evolves into the neural retina, while the outer layer, derived from the proximal portion of the optic vesicle, transforms into the retinal pigment epithelium (RPE). During the embryonic stage, a crucial event known as the optic, choroidal, or fetal fissure emerges, allowing mesenchymal tissue to ingress into the optic cup through invagination along the optic cup and optic stalk. Ordinarily, this fissure undergoes a gradual closure process, typically finalizing by the fifth to seventh week of gestation, with the inferonasal part being the last to seal.

However, when this closure process encounters aberrations or interruptions, it results in the formation of a coloboma.
The term ‘typical coloboma’ is employed to describe the defects predominantly observed in the inferonasal region of the retina, whereas defects occurring in other areas are referred to as ‘atypical colobomas’ (Fig. 1C).

When light enters the eye and hits the abnormal area of the retina where the coloboma is present, it can scatter or reflect differently compared to the healthy parts of the eye. This can result in an irregular or white appearance of the pupil when observed with an ophthalmoscope or in photographs, leading to the characteristic white or grayish reflex seen in leukocoria.

It is worth noting that in certain medical conditions like the CHARGE syndrome, colobomas can be accompanied by a spectrum of other anomalies, encompassing heart defects, choanal atresia, nervous system abnormalities, genital or urinary tract anomalies, or ear malformations.5,11

Retinopathy of prematurity (ROP) is a proliferative retinal vascular disorder that impacts premature infants, particularly those born before 32 weeks of pregnancy and/or with a birth weight lower than 1500 g. The intricate process of retinal angiogenesis commences at around 16 weeks of gestation, gradually extending from the optic disc towards the nasal ora serrata by 36 weeks and reaching the temporal ora serrata (the serrated junction between the choroid and the ciliary body) by 40 weeks of gestation. Consequently, premature infants are born with underdeveloped retinal vascularization.

The delicate balance of this vascularization process can be disrupted, leading to abnormal fibrovascular proliferation at the retinal periphery. In severe cases, this can progress to retinal detachment due to traction, posing a significant risk of blindness.12

Leukocoria manifests in ROP only in its severe forms, particularly when it results in tractional retinal detachment.13

Familial exudative vitreoretinopathy (FEVR) is an inherited vitreoretinopathy characterized by abnormal retinal vascularization (Fig. 2A). This genetic disorder can manifest in different inheritance patterns, including autosomal dominant (involving FZD4 or LRP5 genes), recessive (involving LRP5 gene), or X-linked (involving the NDP gene), depending on the specific gene involved.

A defining feature of FEVR is the presence of an avascular peripheral retina, most notably visible in the temporal periphery, often forming a distinctive V-shaped pattern. In moderate to severe cases, this condition may progress to retinal neovascularization and fibrosis, particularly at the junction between vascular and avascular regions of the retina. Such progression can lead to the traction of the macula and retinal vessels, resulting in varying degrees of macular ectopia, tractional retinal detachment, and impaired vision. In the most severe instances, this traction can culminate in complete retinal detachment.7,14

Myelinated nerve fibers manifest, in fundoscopy examinations, as distinctive gray-white patches with irregular, frayed borders on the anterior surface of the retina. The reflection of light from these gray-white nerve fibers gives rise to leukocoria (Fig. 2B).

During typical prenatal development, myelination of the optic nerve commences at the lateral geniculate body, progresses towards the eye, and concludes posterior to the lamina cribrosa (a sieve-like portion of the posterior sclera) before birth. Nevertheless, in some cases of developmental abnormalities, myelination extends further, anterior to the lamina cribrosa, affecting the nerve fibers within the optic nerve head and retina.

It is important to note that these myelinated nerve fibers are generally considered benign and nonprogressive lesions.15

Ocular toxocariasis is a relatively rare infection caused by the larvae of the nematode parasite *Toxocara canis*, commonly found in dogs. Human infection occurs incidentally when individuals ingest infective eggs present in contaminated soil or from paratenic hosts. Once ingested, these eggs hatch, and the larvae penetrate the intestinal wall, entering the bloodstream and subsequently disseminating to various organs, including the liver, heart, lungs, brain, muscles, and eyes. Ocular toxocariasis primarily manifests in two clinical forms: visceral larva migrans and ocular larva migrans. In the latter, a common presentation involves the formation of granulomas within the retina, often accompanied by varying degrees of vitritis. Key symptoms of this condition encompass decreased vision, ocular pain, photophobia, and the perception of floaters.16 Remarkably, ocular toxocariasis has even been documented in preterm neonates (Fig. 2C).17

- **Ocular toxoplasmosis** arises from an infection with the protozoan parasite *Toxoplasma gondii* and is one of the most prevalent causes of posterior uveitis worldwide. Cats serve as the definitive hosts for *T. gondii*. The classic form of this disease is recurrent posterior uveitis, characterized by the development of unilateral, necrotizing retinitis accompanied by secondary choroiditis. These inflammatory changes are typically located adjacent to a pigmented retinochoroidal scar and are often associated with retinal vasculitis and vitritis. In affected children capable of vocalizing their discomfort, symptoms may include complaints of reduced vision or ocular pain, while parents may observe signs such as leukocoria or strabismus. Ocular toxoplasmosis represents a significant clinical concern due to its potential for vision-threatening complications.18
Astrocytic hamartomas represent benign glial tumors originating from astrocytes within the nerve fiber layer of the retina. Although they are classically linked to systemic phacomatoses like tuberous sclerosis complex and neurofibromatosis, these lesions can also emerge as incidental discoveries in otherwise healthy individuals. They exhibit a wide range of locations within the retina, spanning from the optic disc to the periphery. Clinically, they typically manifest as raised growths with well-defined borders, sporting a distinctive ‘mulberry’ appearance characterized by multiple lobules. Fortunately, complications are rare in cases of astrocytic hamartomas, underscoring their benign nature.

Combined hamartoma of the retina and retinal pigment epithelium represents a benign and pigmented elevation within the retinal and retinal pigment epithelial layers. It is presumed to be congenital. The most prevalent presentation is painless, progressive vision loss, with a higher incidence observed in macular lesions.

Vitreous causes

Early in embryonic development, the intraocular fetal vascular system plays a pivotal role in shaping the lens, vitreous, and retina. This vascular network originates from the optic nerve head, traverses the central vitreous, envelopes the maturing crystalline lens, and ultimately nourishes the anterior segment of the eye. Crucially, the timely regression of this fetal vascular system is essential for establishing a clear optical medium.

However, persistent fetal vasculature (PFV) represents a congenital ocular anomaly wherein this vascular network does not regress as expected, either partially or entirely, for reasons that remain elusive. Diagnosis of PFV typically occurs shortly after birth, highlighting the significance of early recognition. Traditionally, PFV could be divided into three categories based on the location of the vascular abnormalities: purely anterior, purely posterior, and combined PFV. Purely anterior PFV is relatively common and is characterized by cataract, posterior crystalline lens, a shallow anterior chamber and elongation of the ciliary processes. Purely posterior PFV mainly involves the vitreous and the retina and it may manifest as a stalk.

Endophthalmitis is a serious ophthalmological condition characterized by infectious involvement of the vitreous, bearing devastating consequences for vision. In the pediatric population, the severity of this disorder escalates, as children may struggle to articulate or identify their symptoms, potentially leading to diagnostic delays. Clinical manifestations of endophthalmitis encompass a red eye, diminished visual acuity, eyelid edema, ocular discomfort, excessive tearing, or photophobia. This affliction can be categorized as exogenous when pathogens directly enter the eye through mechanisms such as intraocular surgery, penetrating trauma, or contiguous spread from adjacent tissues. Acute postoperative endophthalmitis typically manifests within one to two weeks following surgery. Alternatively, it may manifest as endogenous when infectious agents disseminate hematogenously into the eye from a distant source of infection.

Vitritis denotes inflammation of the vitreous humor. In pediatric patients, it most frequently occurs in conditions such as pars planitis, sarcoidosis, toxocariasis, toxoplasmosis, tuberculosis, Behçet’s disease, or tubulointerstitial nephritis and uveitis (TINU).

Lens causes

A cataract is a condition characterized by an opacity of the lens. If not diagnosed and treated promptly, it can lead to partial or total vision loss. In infants and toddlers, cataracts can manifest across a wide spectrum, ranging from subtle anterior polar cataracts that appear as small opacities in the red reflex to dense, white nuclear cataracts that give rise to a white pupil – a true leukocoria. It is important to note that only white cataracts result in leukocoria, while others may not display this telltale sign but instead attenuate the passage of light through the pupil, thereby reducing the red reflex.

Cataracts in children may manifest in isolation or in conjunction with various underlying conditions. These include chromosomal abnormalities such as trisomy 13, 18, and 21, systemic syndromes like Alport syndrome and Lowe syndrome, as well as diseases like Fabry disease, galactosemia, diabetes mellitus, and Wilson disease. Infections such as cytomegalovirus, rubella, syphilis, toxoplasmosis, and chickenpox, as well as instances of trauma and radiation exposure, can also contribute to cataract development. It is worth noting that cataracts associated with systemic diseases typically affect both eyes in nearly all cases.

The timing of congenital cataract detection plays a pivotal role in shaping post-surgical visual outcomes. Early therapeutic intervention, specifically before six weeks of age for unilateral cases and eight weeks for bilateral cataracts, has been linked to the most favorable visual results.
Anterior chamber and corneal causes

While anterior chamber and corneal conditions can indeed manifest with white color anomalies, it is essential to distinguish them from true leukocoria. In these cases, the white appearance does not originate from the pupil itself or the passage of light through it. Instead, it results from the presence of white structures anterior to the pupil.

Dysgenesis of the anterior segment of the eye represents a complex spectrum of congenital abnormalities affecting the structures at the front of the eye, including the cornea, iris, and lens. These abnormalities arise during embryonic development, leading to structural irregularities and malformations. This group of disorders includes aniridia (partial or complete absence of the iris), Axenfeld-Rieger anomaly, Peter’s anomaly, sclerocornea, and primary congenital glaucoma. Peter’s anomaly, sclerocornea, and congenital glaucoma may present with white opacifications of the cornea.

Peter’s anomaly is a congenital disorder that primarily affects the anterior segment of the eye. It is characterized by a central corneal opacity and is often associated with other ocular defects such as thinning of the cornea, iridocorneal adhesions, and cataract.

Sclerocornea is a rare, non-inflammatory condition characterized by the partial or complete opacification of the cornea, which has a sclera-like appearance. This congenital anomaly is typically bilateral and involves the peripheral cornea, although it can sometimes affect the entire cornea. Management may involve supportive care or surgical intervention, such as a corneal transplant, in certain cases.

Congenital glaucoma is a severe condition that is characterized by elevated intraocular pressure, leads to optic nerve damage, and is associated with symptoms such as photophobia, epiphora, and blepharospasm. Clinical characteristics often include an increase in corneal diameter, corneal edema, and breaks in Descemet’s membrane, known as Haab’s striae. These breaks can cause corneal edema leading to secondary opacification and a whiter color of the cornea.

Corneal opacities that present as a white or gray color of the cornea may also be acquired either by infections, trauma, inflammatory or metabolic conditions. Infections such as herpes zoster, rubella, or Chlamydia trachomatis may lead to corneal scarring. Interstitial keratitis, a non-infectious inflammation of the corneal stroma may also present as a whitish cornea. Birth trauma (Fig. 2D), accidental or surgical trauma produces corneal injury that leads to scarring and leukoma (Fig. 3E). In rare metabolic diseases such as mucopolysaccharidosis corneal clouding may appear by deposition of glycosaminoglycans. Severe vitamin A deficiency may produce xerophthalmia and subsequent corneal scarring.

Pseudoleukocoria

An abnormal red reflex test may originate from various ocular conditions affecting the retinal, vitreous, lens, anterior chamber, corneal, or tear film structures. It is imperative to differentiate leukocoria from pseudoleukocoria. The latter may occur when a child fixates off-axis, resulting in an abnormal light reflex from the optic nerve in the affected eye or in a child with strabismus, where the fundus reflex of the fixing eye appears darker while that of the non-fixing eye appears brighter and lighter.

Pseudoleukocoria can also be caused by anisometropia (significant difference in refractive error between the two eyes). In this case, the eye with greater axial length (more myopic) will have a reduced brightness reflection. This change in brightness can be difficult to assess in clinical practice by untrained clinicians.

Medical history and physical examination

Upon suspicion of an abnormal red reflex, a comprehensive medical history should be compiled, encompassing prenatal, birth, and postnatal history, with a focus on exposures and complications that might be associated with specific causes. Examples include exposure to corticosteroids (which can induce cataracts), congenital infections like cytomegalovirus, toxoplasmosis, or rubella (which can cause chorioretinitis and/or cataracts), and preterm birth (associated with ROP). A meticulous history of medical conditions and medications (e.g., corticosteroids), time course, exposure to puppies or kittens, as well as a history of pica or geophagia (associated with toxocariasis or toxoplasmosis) and detailed ophthalmological family history (e.g., RB, congenital cataract and FEVR) should also be obtained.

The physical examination should meticulously assess dysmorphic features and growth parameters, including head circumference, and evaluate the skin for signs of coagulopathy, trauma, or neurocutaneous disorders. During the ophthalmology consultation, a thorough ophthalmologic examination should be conducted according to the child’s age, encompassing visual acuity testing in each eye, intraocular pressure measurement, pupillary reflex testing, sensorimotor examination, anterior segment examination, dilated fundus examination, and cycloplegic refraction. Parents of these children should also undergo an ophthalmologic evaluation, as they often exhibit similar conditions, albeit in a milder form, as frequently observed in cases of congenital cataracts.
Changes in the visual axis invariably affect visual function. However, changes in the extra-macular retina could result in modifications in the red reflex under certain gaze positions and may not necessarily impact visual acuity. Decreased or lost visual stimuli can disturb efferent pathways, leading to changes in ocular motility and subsequently causing strabismus.

PROGNOSIS AND CONCLUSION
The prognosis of an abnormal red reflex test depends on its etiology. While cases of RB may be life-threatening, contemporary advancements have enabled survival rates to exceed 95% to 98% in industrialized countries. Conversely, these conditions may compromise future visual acuity by inducing amblyopia.9

In conclusion, the red reflex test should be performed on all newborns and children during routine health surveillance visits. Detecting an abnormal red reflex can be pivotal for identifying diseases that threaten sight and even life. Any suspicion requires an expedited evaluation by an ophthalmologist.

AUTHOR CONTRIBUTIONS
JSO, RSS: Data collection, writing and critical review of the manuscript.
SC, GR: Critical review of the manuscript.
AM: Data collection, critical review of the manuscript.
All authors approved the final version to be published.

COMPETING INTERESTS
The authors have declared that no competing interests exist.

FUNDING SOURCES
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES
Table 1 – Causes of an abnormal red reflex test

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Figure 1 – Retinoblastoma (A); Coats disease (B); retinochoroidal coloboma (C)
Figure 2 – Familial exudative vitreoretinopathy (A); myelinated nerve fibers (B); ocular toxocariasis (C); birth trauma with forceps (D)
Figure 3 – Persistent fetal vasculature (A, B); cataract (C, D); corneal leukoma (E)