Leukocoria and the red reflex test

Leucocoria e teste do reflexo vermelho

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ABSTRACT
Until recently, the ophthalmologic examination of newborns in maternity hospitals was not a priority; even today, few hospitals perform this examination adequately. Consequences may be disastrous, because by the time eye alterations are found, the child may have developed permanent loss of visual acuity. The ophthalmologic examination in nurseries, carried out by neonatologists, permits an early diagnosis and referral for effective therapy and adequate development of vision. This study underlines the importance of the red reflex test in newborns and presents the main causes of leukocoria (cataract, retinoblastoma, and retinal and vitreous diseases) to alert pediatricians and neonatologists about this condition. Special emphasis is given to retinoblastoma, a condition affecting 1/14,000 to 1/20,000 live newborns; genetic, clinical, diagnostic, and therapeutic aspects are presented. Early diagnosis of retinoblastoma is essential for reducing morbidity and mortality.

Keywords: Reflex, pupillary/etiology; Eye diseases/complications; Eye manifestations; Diagnostic techniques, ophthalmological

INTRODUCTION
Leukocoria may be a common sign in various ocular conditions – such as cataract, retinoblastoma, and retinal and vitreous diseases – and may be characterized by a whitish pupillary reflex (leukos: white, kore: pupil) that differs from the normal red ocular reflex.

The red ocular reflex appears when a light beam is focused on the eye through the pupil; the light is partly absorbed and partly reflected by the retina back through the pupil, appearing as a reddish-orange reflex characterizing the normal color of the retina and the choroid.

An early diagnosis is possible with the red reflex test, which reduces the morbidity and possibly the mortality of various ocular conditions.

The red reflex test
The red reflex test is used for screening purposes to detect changes in the fundus of the eye and opacities on the visual axis, such as cataract and corneal opacities. This test should be done preferably in a dark room, as papillary miosis due to light makes the test harder to interpret. The child may be seated on his or her parent’s lap or lying on a bed with eyes open, voluntarily if possible. The examiner should be at about 50 cm from the child and should examine the pupils with a direct ophthalmoscope, separately and simultaneously, comparing their reflexes.

The ocular reflex should be visible and symmetrical in color and intensity in both eyes (Figure 1). The reflex color in children with little ocular pigmentation (white race) is reddish-orange; in children with more intense ocular pigmentation (black race), the reflex is darker (reddish-brown).

Examination with midriasis (papillary dilatation) increases the test sensitivity. Dilatation may be attained using eye drops with sympatheticimetic agents (2.5%...
phenylephrin) and/or anticolinergics (1% tropicamide); one drop is administered in each eye 15 to 30 minutes before testing. Although sporadic complications of these medications has been reported – such as increased arterial pressure and heart rate, rashes and contact dermatitis – papillary dilatation has been used routinely in most pediatric patients in ophthalmological offices and neonatal units without complications in most cases, showing that this procedure appears to be safe in children and premature neonates(1).

The red reflex test should be repeated in routine visits up to age 3 years.

Alterations in the red reflex, such as asymmetrical intensity and color, whitish spots, or absent reflexes, may suggest crystalline, retinal or vitreous disease. Any changes in the red reflex should prompt a referral of the child to a more detailed ophthalmological assessment, which should include examination of the fundus of the eye by indirect ophthalmoscopy.

Causes of leukocoria
Leukocoria may be unilateral or bilateral (Figures 2 and 3). The differential diagnosis of leukocoria includes the following diseases: cataract; uveitis; ocular toxocariasis; persistent hyperplastic primary vitreous (PHPV); coloboma; retinopathy of prematurity; Coats’ disease; retinoblastoma.

Cataract
Infantile cataract is one of the main causes of avoidable blindness and sub-normal vision in children(2). This condition arises when the crystalline is partially or fully opaque, on one eye only or bilaterally, decreasing visual acuity.

There may be many causes of crystalline opacity, such as congenital ocular malformation, intra-uterine infection (rubella, cytomegalovirus, chickenpox, toxoplasmosis), genetic syndromes (the Down, Patau and Lowe syndromes), metabolic diseases (galactosemia, hypoparathyroidism, hypoglycemia), heredity (dominant autosomal inheritance is more common, but there have been reports of recessive autosomal and X-linked inheritance), medications (corticosteroids), and radiation; it can also be an acquired condition (trauma, secondary to uveitis) or have idiopathic causes(3).

The cause of vision loss in most cases is irreversible amblyopia. Congenital cataract should be detected and treated early for eyesight to develop normally. Thus, all children should undergo the red reflex test at birth.

Children with cataract may present leukocoria, low visual interest (especially when the condition is bilateral), strabismus, poor visual fixation on objects, and nystagmus, the latter resulting from early visual deprivation, and carrying a poor visual prognosis.

Treatment of partial cataract may be conservative, depending on the scope and on the child’s visual acuity. Surgery is done in cases of marked loss of vision or if there is total cataract. The visual prognosis depends on how early the diagnosis was made and the treatment was started.

Uveitis
Uveitis is an inflammation of any uveal tract segment, comprising the iris, ciliary body and choroid. Uveitis
may be anterior, intermediate or posterior, according to the site.

Uveitis may be associated with leukocoria, as in cases of chronic anterior uveitis, which is commonly due to juvenile rheumatoid arthritis in pediatric patients. It may progress to cataract and leukocoria. In cases of posterior uveitis, leukocoria may be associated with vitreitis (progressing to vitreous opacity), choroiditis or retinitis. Infections such as toxocariasis, syphilis, candidiasis, toxoplasmosis, rubella, CMV, and herpes simplex (TORCH) should be excluded in these cases\(^4\).

**Ocular toxocariasis**

Toxocariasis is caused by a parasite (*Toxocara canis*) endemic in dogs; it is also the cause of visceral *Larva migrans* infection.

Human infection takes place after a person consumes earth contaminated with parasite eggs or food contaminated with dog feces. In the human intestine, the egg gives rise to the nematode larva, which penetrates the wall of the intestine. There is systemic infestation of various organs – liver, lungs, brain and eyes – through the bloodstream and lymphatic system.

In the eye, nematodes induce focal choroidal inflammation and granuloma formation; if they reach the vitreous cavity, nematodes may cause intense vitreitis associated with choroiditis that results in endophthalmitis (Figure 4).

The most frequent clinical manifestations of ocular toxocariasis are: chronic endophthalmitis, granulomas in the posterior pole or peripheral granulomas. Granulomas are whitish rounded lesion consisting of fibrin, epithelioid cells, lymphocytes, giant cells and numerous eosinophils. Complications may ensue, such as retinal detachment and vitreous-retinal traction areas.

These conditions generally involve one eye only; bilateral involvement is rare. The mean age for presenting the disease is 7 to 8 years, ranging from 2 to 9 years; visceral *Larva migrans* infection, on the other hand, occurs at ages 2 to 3 years\(^5\). The diagnosis is based on clinical findings and specific laboratory tests (ELISA).

Medical therapy consists of topical or systemic corticosteroids, depending on the degree of intraocular inflammation. Single use of antihelminthic therapy, such as thiabendazol, is questionable, since larval death increases inflammation that may result in ocular damage. It should therefore be used together with corticosteroids. Surgery is reserved for retinal detachment cases\(^6\).

**PHPV**

PHPV is a generally unilateral congenital, non-hereditary ocular malformation that is usually not associated with other congenital defects, except for cataract formation. It results from persistent fetal vascularization – the fetal hyaloids system – that usually disappears by the 8th month of pregnancy.

In most cases, the fibrovascular membrane fed by the persistent hyaloid artery adheres to the posterior capsule of the crystalline. In more severe cases, fibrovascular invasion of the crystalline may ensue, leading to cataract, a shallow anterior chamber, and closed angle glaucoma. Central or peripheral retinal detachment may also be present. The most feared complications are closed angle glaucoma and intraocular hemorrhage, which may originate from bleeding in the fibrovascular membrane in the retrocrystalline space\(^7\).

PHPV may be associated with microphthalmia. The affected eye is generally smaller than the contralateral eye; in some cases, this difference is only visible on ocular ultrasound. Documenting and diagnosing microphthalmia is important to exclude retinoblastoma, which may occasionally be associated with PHPV.

Early therapy includes cataract surgery and removal of the fibrovascular membrane. The prognosis for vision depends on how much the posterior segment is involved\(^8\).

**Optic nerve coloboma**

This is a congenital disease due to an altered embryological development of the optic nerve in about 1 of 12,000 patients. It is probably due to incomplete closure of the embryonic cleft that develops from the optic vesicle when the ocular globe is formed.
The clinical features are: fully or partially increased papillary cupping, a widened papillary area, a whitish surface, and retinal vessels entering and exiting the borders of this defect. These findings may be associated with coloboma of the iris and the retina\(^6\).

Colobomas may be unilateral or bilateral; visual acuity may range from normal to absence of light perception. In some cases, generally adults, the condition may be accompanied by regmatogenic retinal detachment requiring surgery (vitrectomy through a \textit{pars plana} approach).

Various systemic conditions have been associated with ocular colobomas, such as cardiovascular, neurological, dermatological, gastrointestinal, genitourinary, and musculoskeletal diseases. A classical example is the CHARGE syndrome, which manifests as: coloboma, cardiopathy, choanal atresia, mental and development retardation, genital hypoplasia, and ear malformations with hearing loss\(^{10}\). Children with colobomas should be examined systemically to investigate these conditions.

**Retinopathy of prematurity**

Retinopathy of prematurity is a retinal vascular disease of preterm newborn, especially those below 1,500 grams and 32 weeks gestational age at birth.

Retinal vascularization is complete by 42 weeks gestational age; thus, the peripheral retina is not fully vascularized at birth. After birth, vascularization of the peripheral retina proceeds normally. However, if this process does not occur, anomalous vessels may grow and result in retinopathy of prematurity.

In most cases, retinopathy of prematurity regresses spontaneously, with full resolution in milder cases.

Leukocoria may be associated with more advanced cases, when there is retinal detachment. The prognosis of vision is poor in this phase; the most important risk factor is extremely low birth weight.

Cryotherapy or laser photocoagulation of avascular retina, when performed at the appropriate time, are treatments that induce disease regression, avoiding retinal detachment in most cases.

**Coats’ disease**

This is an idiopathic disease described by George Coats in 1908. It is characterized by retinal vessel telangiectasia and engorgement with intra- and sub-retinal exudation (Figure 5). It is thought that exudation is due to leaking of anomalous vessels.

Coats’ disease may present in an adult and a juvenile form. Males are more often affected in the juvenile form; the disease is unilateral in 80% of cases. There is no race predominance or genetic transmission. The most frequent age of diagnosis is 8 to 10 years\(^{11}\).

Clinical manifestations may include poor vision, strabismus, and leukocoria. The typical finding on the fundus of the eye is a yellow exudate rich in lipids, and engorged, tortuous vessels with telangiectasia, and occasionally revascularization of retinal vessels.

This disease may progress at a variable rate. Acute exacerbation may alternate with non-progression periods. Spontaneous remission has been reported, albeit rare. Generally, as the disease progresses, intense exudation results in serous retinal detachment. In more severe cases, the eye may undergo bulbar atrophy (\textit{phthisis bulbi}) secondary to complications such as retinal hemorrhage and neovascular glaucoma.

The purpose of therapy is to preserve or improve visual acuity; in advanced cases, where loss of vision is irreparable, the aims are to preserve the remaining retina and the eye. Interventions focus on the vascular leakage area to obliterate vessels so that the exudate is reabsorbed; this may be done with cryotherapy or laser photocoagulation.

Results for vision vary, depending on the extent of the disease and the site of retinal alterations. The prognosis for vision is poor if the macula (central retina) is involved.

**Retinoblastoma**

Retinoblastoma is a tumor that originates from immature retinoblasts in the neural retina; it is the most frequent intraocular tumor in children. The incidence
ranges from 1/14,000 to 1/20,000 live births, depending on the country\(^{(12)}\). Over 90% of cases are diagnosed before age 5 years.

**Genetics**

Retinoblastoma was one of the first malignancies to be associated with genetic alterations. The retinoblastoma gene (gene RB1) is located on the long arm of chromosome 13 on region 14 (13q14). This is a tumor suppressant gene that codes a protein (p RB) responsible for controlling the cell cycle between phases G1 and S to inhibit cell proliferation.

Tumor growth requires two mutated retinal cell RB alleles. These mutations are two isolated events\(^{(13)}\). The first mutation (or first event) may be somatic (non-inherited) or germinal (inherited), which affects the presentation of the disease. The second mutation is always somatic.

Mutation of both alleles in non-inherited tumors occurs in a single retinal cell, forming a single tumor in one eye (unifocal and unilateral disease). This form comprises about 60% of all cases, and generally arises in the second year of life. The first mutation in the inherited form of the disease occurs in a germ cell; the mutate allele, thus, is present in all body cells, including retinal cells. Mutation of the second allele (second event) may take place in some of these retinal cells and give rise to multiple tumors located in one or both eyes of children (multifocal unilateral or bilateral disease). This form is generally diagnosed in the first year of life, and comprises about 40% of retinoblastoma cases. The latter patients, having a mutated allele in all body cells, have a higher chance of developing other malignancies during life, particularly if they are exposed to radiation\(^{(14)}\).

**Clinical presentation**

The most frequent clinical presentation of retinoblastoma is leukocoria (from 60 to 80% of cases), also known as “cat’s eye reflex”\(^{(15)}\). Leukocoria may be unilateral or bilateral, according to each type of retinoblastoma in children (Figures 6 and 7).

Other common presentations are strabismus, red eyes, enlarged ocular globe due to increased intraocular pressure, and loss of vision. Less common forms are aseptic orbit cellulitis due to tumor necrosis, altered color of the iris (heterochromia), intraocular bleeding (vitreous or hyphema hemorrhage), and pseudouveitis. Retinoblastoma may be diagnosed in a routine examination, especially in cases with a family history of the disease.

Advanced disease, where tumors invade the orbit or the optic nerve, may present with ocular proptosis and restricted eye motility.

**Diagnosis**

Early diagnosis of retinoblastoma is essential to reduce disease morbidity and mortality. Initial lesions are more easily treated and result in a higher cure rate and conservation of the eye and vision. Continued education of pediatricians and general ophthalmologists – and red reflex testing with dilated pupils – at maternity hospitals and in routine pediatric examinations during the first three months of life are important measures for early detection of retinoblastoma and other ocular diseases in children.

Fundus of the eye examinations should be done since birth in patients with a family history of retinoblastoma.

Most patients are referred to special care when symptomatic. In these cases, a detailed clinical history and fundus of the eye examinations are initial and fundamental steps for diagnosis.

Image tests may help the diagnosis; ultrasound provides information about the size of the lesions and may find calcification within the tumor – a typical sign of retinoblastoma. Magnetic resonance imaging provides information about extracocular involvement and
invasion of the optic nerve; it also helps differentiate retinoblastoma from other ocular conditions, such as Coats’ disease. Computed tomography is the best exam for detecting calcium within a tumor; nevertheless, it should be used parsimoniously, because exposure to radiation may increase the risk of a second neoplasm, particularly in patients with germinal retinoblastoma(16).

Invasive procedures, such as fine needle biopsies, should not be done in suspected retinoblastoma cases, since such procedures increase the possibility of extraocular tumor spread, worsening the prognosis.

**Classification of the intraocular disease**

Use of chemotherapy in place of external beam radiotherapy as the treatment of choice for intraocular retinoblastoma has led to a new classification for this disease. International efforts in 2001 generated the International Classification for Intraocular Retinoblastoma, which comprises five groups based on the natural history of the disease(17). Groups A to E reflect disease progression and the prognosis after chemotherapy (Charts 1 and 2).

**Chart 1. International Classification for Intraocular Retinoblastoma**

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Tumors confined to the retina, located in at least 3.0 mm from the fovea and 1.5 mm from the optic disk. Lesions smaller than 3.0 mm in height or basal diameter. Absence of vitreous or subretinal seeding.</td>
</tr>
<tr>
<td>Group B</td>
<td>Tumors larger than those in group A, in any site. Absence of vitreous or subretinal seeding. Presence of subretinal fluid up to 5.0 mm from the base of the lesion.</td>
</tr>
<tr>
<td>Group C</td>
<td>Tumors with focal vitreous or subretinal seeding. Up to one quadrant of subretinal fluid.</td>
</tr>
<tr>
<td>Group D</td>
<td>Eyes with diffuse vitreous or subretinal seeding and/or significant endophytic or exophytic disease. Avascular masses. More than one quadrant of subretinal fluid.</td>
</tr>
<tr>
<td>Group E</td>
<td>Eyes that have suffered definitive anatomical and functional changes. They present one or more than the following alterations: irreversible neovascular glaucoma; massive intraocular hemorrhage; aseptic orbital cellulitis; tumor touching the lens; diffuse retinoblastoma; atrophic eye.</td>
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**Chart 2. Prognosis of retinoblastoma**

<table>
<thead>
<tr>
<th>Group</th>
<th>Prognosis</th>
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</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Very low risk</td>
</tr>
<tr>
<td>Group B</td>
<td>Low risk</td>
</tr>
<tr>
<td>Group C</td>
<td>Moderate risk</td>
</tr>
<tr>
<td>Group D</td>
<td>High risk</td>
</tr>
<tr>
<td>Group E</td>
<td>Very high risk</td>
</tr>
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**Treatment**

The treatment of retinoblastoma is complex and requires a trained multidisciplinary team for healthcare at all stages of therapy. The aims of therapy are to save the child’s life and, secondarily, to conserve the eye and vision.

There are different options available for each individual case. Local and systemic factors should be taken into account when choosing the treatment, such as the intraocular tumor size and site, extraocular involvement, laterality, the prognosis for vision, the patient’s clinical status, disease spread, and others.

Current therapies of choice for intraocular disease are chemotherapy through different routes (endovenous, subconjunctival and intra-arterial), local cryotherapy and laser therapy, radiotherapy (teletherapy and brachytherapy), and enucleation (surgical removal of the eye)(18).

Chemoreduction has changed the approach to retinoblastoma; it has become the first choice in most cases(19-21). Chemoreduction may use an endovenous approach with various drug protocols in six monthly cycles. After the tumor is reduced, treatment may be completed with local therapy, such as cryotherapy, laser thermotherapy, and brachytherapy.

External beam radiotherapy is less and less used; it is recommended in cases where tumor cells have spread to the vitreous cavity and/or the subretinal space that could not be controlled previously by chemotherapy(22). Complications include ocular alterations such as cataract, radiation retinopathy, facial hypoplasia due to bone atrophy, and an increased risk of a second neoplasm in patients with germinal retinoblastomas.

Enucleation is the first treatment in patients with advanced intraocular tumors with anatomical and functional alterations(23). Enucleation as secondary treatment may be used when there is no response to the initial therapy. The eye should be removed with the largest possible segment of the optic nerve, which is considered the most important surgical margin.

High-dose chemotherapy and external beam radiotherapy are the options in extraocular disease(24). Exenteration is becoming less used in these cases.

**REFERENCES**


