Infantile Leukocoria: the white pupil
Charlotte Buscombe1, Sophie Headland2

Abstract
Leukocoria (a white pupil) in a child can signify serious intraocular disease. This educational review uses an anatomical framework to review the most common causes of infantile leukocoria, considering the anterior chamber/lens, vitreous, retina and optic nerve in turn. Through adopting such a systematic approach, it is hoped clinicians faced with this unfamiliar clinical sign will be better enabled to formulate possible differentials, and to correctly judge the urgency of referral to ophthalmology required.

Keywords: leukocoria, retinoblastoma, cataract

Introduction
Leukocoria is the clinical finding of a white pupillary reflex. The term has greek semantic roots, “leukos” meaning white and “kore” meaning pupil. Infantile leukocoria is often first detected by parents, either directly, or becoming apparent on flash photography.1 Whilst transient leukocoria can simply be caused by the reflection of a normal optic disc, a persistent white pupil can signify serious intraocular disease, most ominously exposing an underlying retinoblastoma.1,2 This educational review uses an anatomical framework to review the most common causes of infantile leukocoria which clinicians should be aware of, systematically considering anterior chamber/lens, vitreal and retinal causes in turn.

The Normal Pupillary Reflex
The normal ‘red’ pupillary reflex seen on ophthalmoscopy occurs as light is reflected off a healthy retina. Leukocoria occurs when the incident light is instead reflected off a lesion within the pupillary area on direct fundal illumination.1 Causes of leukocoria can be classified anatomically, as outlined in Table 1.

The red reflex test is performed by holding a direct ophthalmoscope close to the examiner’s eye with the lens power set at “0”. In a darkened room, standing approximately one meter away from the patient, the ophthalmoscope light should be projected onto both eyes simultaneously and then each eye alternately. To be considered normal, a red reflex should emanate from both eyes and be symmetric in character.
Anterior Chamber/Lens Causes

Cataract
Dense cataracts obscure fundal views and cause the appearance of a white pupil (Figure 1A). Congenital cataracts may be present at birth or appear in early infancy. Often there is a strong family history on questioning, with an autosomal dominant inheritance pattern, although other causes include congenital infections, metabolic disorders or chromosomal abnormalities. Orbital trauma or uveitis can also precipitate rapid cataract development. In the developing world, ‘white pupil campaigns’ strive to highlight the global burden of cataract-related visual loss.

Vitreous Causes

Persistent Fetal Vasculature
In normal embryonic development, after four months gestation, the primary vitreous and hyaloid vascular system involute. Persistent fetal vasculature (formerly known as persistent hyperplastic primary vitreous) results from a failure of this process and is characterised by a rudimentary vascular stalk remaining in the vitreous extending to the optic nerve, usually associated with an opacity in the posterior lens. It is typically unilateral and associated with microphtalmia, causing leukocoria through retrolental fibroplasia (abnormal retinal vasculature growth) resulting in retinal detachment or cataract.

Vitreous Haemorrhage
If a vitreal haemorrhage organises into a dense clot it can cause leukocoria.

Uveitis
Uveitis can cause leukocoria due to abnormal retinal reflections, the presence of inflammatory cells or the development of cataracts.

Retinal Causes
Retinal pathology accounts for the majority of presentations with leukocoria, ranging from benign congenital abnormalities to life-threatening retinoblastoma.

Retinoblastoma
Retinoblastoma is a highly malignant neoplasm arising in primitive photoreceptor cells of the retina, associated with a tumour suppressor gene. Although relatively rare, with an annual incidence of 11 per million in children up to four years of age, it is the most common intraocular tumour of children and accounts for 3% of total childhood cancer. It threatens those with the longest potential lifespan, carrying an overall mortality rate of approximately 15% in some studies.

Leukocoria is the most common presenting sign (Figure 1B). Studies suggest it is the underlying diagnosis accounting for up to half of infantile leukocoria presentations. Other clinical findings may including strabismus, inflammation resistant to treatment, hyphema, hypopyon, vitreous haemorrhage, proptosis, glaucoma and orbital pain. A high degree of clinical suspicion is required, with appropriate further investigations including ocular ultrasonography and magnetic resonance imaging. With early diagnosis, complete cure is possible.

Table 1 | Differential diagnosis of leukocoria by anatomical location

<table>
<thead>
<tr>
<th>Anterior Chamber/Lens</th>
<th>Cataract</th>
<th>Uveitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitreous</td>
<td>Persistent Fetal Vasculature</td>
<td>Vitreal Haemorrhage</td>
</tr>
<tr>
<td>Retina</td>
<td>Retinoblastoma</td>
<td>Retinopathy of Prematurity</td>
</tr>
<tr>
<td>Optic Nerve</td>
<td>Optic nerve coloboma</td>
<td>Myelinated Nerve Fibres at Disc</td>
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Retinopathy of Prematurity (ROP)
Innovations and advances in neonatal care continue to improve survival and outcomes for infants at increasingly earlier gestational ages. ROP is a proliferative neovascularisation which occurs due to incomplete pre-delivery vascularisation of the retina. Neovascularisation can extend into the vitreous causing tractional retinal detachment and subsequent leukocoria. Elucidating an obstetric history helps evaluate this cause of leukocoria, for ROP occurs with increasing frequency at decreasing gestational age.

Toxocariasis
Toxocariasis, or visceral larva migrans, is a rare infection caused by roundworms from either dogs or cats. The inflammatory response to these parasites often localises to the eye, causing uveitis, endophthalmitis or chorioretinitis. The chorioretinitis causes fairly characteristic subretinal granulomas, whose whitish appearance results in leukocoria.

Coat’s Disease
Coat’s disease is characterised by three major features: retinal telangiectasias, gross retinal exudates with a predilection for the macula, and exudative retinal detachment. The exudates can cause a luminous leukocoria. Coat’s disease, and persistent fetal vasculature are the most common benign lesions to mimic retinoblastoma.

Coloboma
Congenital coloboma are embryological developmental defects. Both retinal coloboma (typically seen in the inferonasal retina) and optic nerve coloboma can cause leukocoria. Other optic disc abnormalities such as a ‘morning glory disc’ or myelinated nerve fibres are also potential causes.

Conclusion
Persistent infantile leukocoria should always be taken seriously and considered to signify serious ocular disease until proven otherwise. This review has outlined a systematic method of evaluating the potential causes of leukocoria according to anatomical location within the eye. This framework can aid clinicians faced with this unfamiliar clinical sign. Given malignant retinoblastoma is the leading underlying cause in this age group, an urgent referral for specialist ophthalmic review should be made, remembering early diagnosis and treatment is imperative to save vision and indeed, life. Moreover, it is important to emphasise that parents noticing a white pupil should seek medical attention and education to this effect may indeed become increasingly important as progressive digital software facilitates greater photographic manipulation and may potentially mask the typical publicised appearance.

Figure 1 | Leukocoria. (A) A child with bilateral cataracts. (B) A child with leukocoria secondary to retinoblastoma. (C) Coat’s Disease. Image demonstrates gross sub-retinal exudates with a resultant total retinal detachment. Images from Wiki commons.
References


LEARNING POINTS

- The normal ‘red’ pupillary reflex occurs as light is reflected off a healthy retina and can easily be checked with a direct ophthalmoscope held at arms length in clinic

- A white pupil (leukocoria) occurs when the incident light is instead reflected off a lesion within the pupillary area and can herald sinister underlying pathology, requiring prompt referral

- Leukocoria can result from a wide range of pathologies, commonly including cataract, retinal vascular disorders, retinal detachment, toxocariasis, benign developmental abnormalities and most ominously, retinoblastoma