An Approach to a Child with Leukocoria

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The term leukocoria means “white pupil” (from the Greek “leukos” meaning white and “kore” meaning pupil) and is the name given to the clinical finding of a white pupillary reflex (Figure 1). Leukocoria can be caused by abnormalities in the lens (e.g. cataract), vitreous (e.g. Persistent hyperplastic primary vitreous, haemorrhage), or retina (e.g. retinoblastoma). It can be the initial manifestation of a wide spectrum of intraocular and systemic disease processes. The differential diagnosis can be narrowed through a complete clinical and family history and a thorough ophthalmic examination.

Although transient leukocoria is occasionally caused by the reflection of a normal optic disc, all children with newly discovered leukocoria should be referred promptly to an ophthalmologist to exclude retinoblastoma and other life-or sight-threatening conditions.

The evaluation of the child with leukocoria and a brief discussion of the common causes of leukocoria in children are presented here.

Causes of Leukocoria

The common causes of leukocoria in children include:\n
- Retinoblastoma (RB)
- Persistent hyperplastic primary vitreous (PHPV)
- Coats disease
- Toxocariasis
- Cataract
- Vascular causes
  - Retinopathy of prematurity
  - Incontinentia pigmenti
- Congenital/developmental anomalies
  - Large coloboma (fissure or cleft) of choroid or optic disc
  - Retinal dysplasia
  - Juvenile retinoschisis
  - Norrie’s disease
  - Combined hamartoma of retina and RPE
- Other tumours
  - Medulloepithelioma
  - Retinal astrocytoma

Workup of a patient with leukocoria

Algorithm for differential diagnosis of a patient with leukocoria is shown in flowchart.

History

- Age of presentation
  - Birth (PHPV)
1-3 years (RB)
- Preschool and school going children (Coats, Toxocara)

- Sex
  - Male (Coat’s, Norrie’s disease, Juvenile retinoschisis)
  - Female (Incontinentia pigmenti)

- Birth history
  - Low birth Weight (ROP)
  - Trauma (Congenital cataract, retinal detachment)

- Family history
  - None (PHPV, Coat’s, Toxocara)
  - AD (RB)
  - Sex linked recessive (Norrie’s, juvenile retinoschisis)
  - Sex linked Dominant (Incontinentia pigmenti)

- Antenatal history
  - Gestational age (ROP)
  - Maternal health (TORCH syndrome)

Examination
Complete ocular examination including examination under anaesthesia (EUA) in young and uncooperative children should be done. In addition to examination of the ocular adnexa and anterior segment, both fundi must be visualized for 360 degrees to detect tumours or other pathology that may be located in the peripheral retina. EUA is often required and may facilitate the performance of computed tomography (CT) or magnetic resonance scan, ultrasonography, fundus photography, laboratory and serologic testing and lumbar puncture. Look for under mentioned features specifically-

- Measure corneal diameters and axial length (look for small eye)
- Iris neovascularisation
- Pupils- Look for any RAPD
- Lens- look for type, laterality, extent and location of cataract
- Look for any vitreous seeding/ persistent foetal vasculature
- Dilated fundus examination- A dilated fundus examination using the indirect ophthalmoscope is essential in the evaluation of children with leukocoria.
The examination should assess:

- Status of the retina (e.g., retinal detachment).
- Presence of retinal vascular abnormalities and/or exudate (as may occur in Coats disease).
- Size, location, and number of tumours, if present.

Any or all of the following may be helpful in diagnosis and planning treatment.

- **B scan ultrasonography** - especially if there is no view of fundus. Look for any tumour/vitreous seeding/retinal detachment/calcification. Retinoblastoma appears as acoustically solid tumour with high internal reflectivity and intralesional calcification (Figure 2).

- **CT Scan** - look for calcification (RB) and optic nerve, orbital and CNS involvement (Figure 3)\(^1\)\(^2\).

- **MRI** - it can detect optic nerve involvement (RB), intracranial extension and pinealoblastoma (RB) although it doesn’t show calcification (Figure 4)\(^3\)\(^6\).

- **LDH activity** - if the LDH activity is raised in aqueous relative to serum level, it is suggestive of retinoblastoma\(^7\).

**Retinoblastoma**

It is most common primary malignant intraocular tumour of childhood. It arises from retina and appears as a white, nodular mass that breaks through the internal limiting membrane into vitreous (endophytic), as a yellowish subretinal mass lesion often underlying a serous retinal detachment (exophytic) or as a diffusely spreading lesion (Diffuse infiltrating) (Figure 5). Iris neovascularisation is common. Pseudohypopyon and vitreous seeding may occur. Cataract is uncommon and eye is normal in size\(^8\). It may be unilateral/bilateral, unifocal/multifocal. Average time of diagnosis is 18 months (12 months for bilateral and 24 months for unilateral cases). A family history is elicited in about 10% of cases and is autosomal dominant in inheritance.

**Persistent hyperplastic primary vitreous**

It is developmental ocular abnormality consisting of a varied degree of glial and vascular proliferation in vitreous cavity\(^9\). There is failure of structures in primary vitreous to regress. It is usually associated with microphthalmos and is unilateral. In anterior form typically there is a membrane behind the lens that may cause traction of ciliary processes which may be elongated. It is a progressive condition with...
catact present at birth or early in life. Membrane and lens may rotate anteriorly and result in secondary glaucoma. Posterior form of PHPV includes a persistent hyaloid artery with a large stalk issuing from the optic disc. Tractional retinal detachment may be seen in advanced cases of posterior form. There is no family history.

**Congenital cataract**

The main causes of infantile cataract are genetic, metabolic, prematurity and intrauterine infections. Other causes of childhood cataract include trauma, drug-induced cataract, radiation therapy and cryo-application or laser therapy for retinopathy of prematurity. Trauma is one of the commonest causes of unilateral cataract in the developing countries. Bilateral cataracts occur commonly due to the long-term use of topical or systemic steroid therapy. In industrialized countries, in approximately 50% of bilateral cases and virtually all of the unilateral cases, the underlying cause cannot be determined (Figure 6).

**Coats disease**

Coats disease is defined by the presence of vascular dilatations (retinal telangiectasia), including ectatic arterioles, microaneurysms, venous dilations (phlebectasias), and fusiform capillary dilatations, frequently associated with exudative retinal detachment\(^{10,11}\). Despite the presence of retinal capillary nonperfusion shown by angiography, posterior segment neovascularization is distinctly unusual. The abnormal vessels are incompetent, resulting in the leakage of serum and other blood components, which accumulate in and under the retina. Any portion of the peripheral and macular capillary system may be involved. Variation in the clinical findings is wide, ranging from mild retinal vascular abnormalities and minimal exudation to extensive areas of retinal telangiectasia associated with massive leakage and exudative retinal detachment, as may be seen in children presenting with leukocoria.

This retinal condition is not hereditary and is not associated with systemic vascular abnormalities, even though a gene has been located on chromosome 4. Entities such as retinitis pigmentosa and others may occasionally be associated with retinal telangiectasia. Usually unilateral and there is a marked male predominance (85%). Gradual progression with increasing exudation occurs over time. The severity and rate of progression appear greater in patients under the age of 4 years, in whom massive exudative retinal detachment with retina opposed to the lens may simulate retinoblastoma. Therefore, Coats disease is included in the differential diagnosis of leukocoria.

Patients with peripheral areas of leaky vascular anomalies typically present with lipid deposition in an otherwise angiographically normal macula, as hard exudate tends to accumulate in the macula. Similar findings seen in adults probably represent late decompensation of pre-existing vascular anomalies. Occasionally, a submacular lipopigmentation or subretinal fibrosis is the initial finding.

For milder cases of lipid exudation, diabetic retinopathy, BRVO, juxtafoveal retinal telangiectasia and radiation retinopathy may be considered.

Treatment of Coats disease generally consists of photocoagulation, cryotherapy, and, in severe cases, retinal reattachment surgery. Photocoagulation and cryotherapy are effective in obliterating the vascular anomalies and in halting progression. Multiple treatments may be necessary and long-term follow-up is important to detect recurrences.

**Retinopathy of prematurity**

Innovations and advances in neonatal care continue to improve survival and outcomes for infants at
Early lensectomy, vitrectomy and retinal repair have been 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.

**Toxicocariosis**

Toxicocariosis 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.

**Norrie’s disease**

Norrie’s disease, a congenital progressive oculo-acoustic-cerebral degenerative condition is a rare X-linked recessive disorder. Norrie’s disease must be considered in male infants with bilateral retro-lental masses. All the affected patients of Norrie’s disease are blind since birth. Mental subnormality occurs in about one third of cases and 25-30% develop a sensory neural deafness. Retinal dysplasia characterised by severe hypoplasia of the inner retinal layers and hyperplasia of the retinal pigment epithelium has been described as the characteristic histological features of Norrie’s disease. Iris atrophy and shallow anterior chamber are typical of Norrie’s disease.

The clinical diagnosis of sporadic Norrie’s disease is possible. The better understanding of extra-ocular signs of Norrie’s disease has helped in establishing the diagnosis of the disease, even in the absence of family history. Degenerative changes in the cerebrum and in the acoustic nerves are responsible for mental retardation and neurosensory loss.

Early lensectomy, vitrectomy and retinal repair have been advocated before total retinal detachment and contraction occurs. Prognosis is poor and phthisis bulbi usually occurs inspite of early treatment.

**Coloboma**

Congenital coloboma is 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.

**Incontinentia pigmenti (Bloch-Sulzberger syndrome)**

Incontinentia pigmenti is a rare genodermatosis, has X-linked dominant inheritance pattern and is usually lethal to male fetuses. Ocular features include abnormal peripheral vasculature, gliosis and tractional retinal detachment. In addition skin involvement occurs in all patients. Additionally, other ectodermal tissues may be affected, such as the central nervous system, hair, nails and teeth.

**Retinal astrocytoma**

A sessile to slightly elevated, yellowish white retinal mass that may be calcified and is often associated with tuberous sclerosis and rarely neurofibromatosis. It may occur on the optic nerve head (giant drusen) in patients with tuberous sclerosis.

**References**