·Review·

# Eye pathologies in neonates

*Nyaish Mansoor[1], Tihami Mansoor[1], Mansoor Ahmed[2]*

[1]Leeds School of Medicine, University of Leeds, LS2 9JT, United Kingdom

[2]Queen's Hospital, Burton Upon Trent, DE13 0RB, United Kingdom

**Correspondence to:** Mansoor Ahmed. Queen's Hospital, Belvedere Road, Burton Upon Trent Staffordshire DE13 0RB, United Kingdom. mansoorlmc@yahoo.com

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## Abstract

• **In the United Kingdom, newborn assessment incorporates a screening eye examination for any structural abnormalities, observation of neonate´s visual behaviour and direct ophthalmoscopy examination looking for red reflex. Early identification and immediate management of eye related pathologies should commence soon after birth as early diagnosis and prompt intervention may have significant impact on the prognosis for many potentially blinding but treatable disorders such as congenital cataracts and retinoblastoma. If left undetected and untreated, such problems may potentially lead to irreversible damage to the vision which persists into adulthood resulting in lack of self –confidence together with difficulties in educational attainment and job opportunities.**

• **KEYWORDS:** newborn; eye; screening; congenital cataract; retinoblastoma

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## INTRODUCTION

Eyesight is regarded by many as the most important of the basic senses. Loss of vision can have huge repercussions on a child's quality of life. A significant number of congenital and acquired eye disorders can affect newborn infants. As some of these are extremely rare, inclusion of each and every eye related condition is beyond the scope of this manuscript. Hence, in this review article, we have chosen to focus only on the most prevalent neonatal and infantile ophthalmological disorders and their associated findings.

In the United Kingdom (UK), parents of all newborn babies are offered Newborn Infant Physical Examination (NIPE) within 72h after birth [1]. Eye examination in the newborn (which encompasses NIPE) involves careful observation of the eye anatomically from external to internal structures [2]. Associated facial features are noted for any abnormality including symmetry and eyelid abnormalities. Further examination includes opening the eyelids and inspecting the globe for symmetry and structural anomalies. Direct ophthalmoscopy is performed to check for light reflex and red reflex. This screening examination is important as the prognosis of certain eye disorders depends on early detection and intervention in order to prevent long-term complications[3].

## CATARACT

Various causes of leukocoria (white pupillary reflex) include congenital cataract (most common), retinoblastoma, retinopathy of prematurity, vitreous haemorrhage, retinal detachment and persistent foetal vasculature[4].

**Incidence** The incidence stands at about 3 in 10 000 population which equates to 200-300 children being born with congenital cataract each year in the UK[5].

The most common cause of congenital cataract is genetic mutation making up to 25% of all cases which are usually autosomal dominant in pattern. Other causes include chromosomal abnormalities, metabolic disorders and as part of congenital infection syndrome [6]. Chromosomal abnormalities associated with congenital cataracts include both Down's syndrome (trisomy 21) and Edwards Syndrome (trisomy 18). Galactosaemia, a metabolic disorder, causes congenital cataract which is characterised by its specific central oil-droplet like morphology. Other metabolic disorders comprise Wilson's disease, hypocalcaemia, hypo/hyperglycaemia and Lowe syndrome. Intrauterine infections that involve congenital cataract in their presenting symptoms include rubella, toxoplasmosis, cytomegalovirus (CMV), syphilis and varicella zoster virus (VZV)[7].

**Clinical Manifestation** Apart from absent red reflex, other presentations of congenital cataract include nystagmus and a baby who is unaware of his/her surroundings or unable to fix & follow.

**Management** During NIPE, if a congenital cataract is suspected, as with other suspected ophthalmic pathologies, a referral should immediately be made to an ophthalmologist for further examination and management. A congenital cataract may not always be treated surgically if the cataract does not reasonably affect vision. However, most cases are bilateral which do require surgery involving anterior capsulorhexis, aspiration of lens material, capsulorhexis of the posterior capsule, limited anterior vitrectomy and intraocular lens implantation.

The prognosis for vision is significantly better if congenital cataracts are diagnosed and treated before the age of 2mo [8-9]. On the other hand, if the diagnosis is delayed, severe and irreversible amblyopia may result.

**GLAUCOMA**

Primary congenital glaucoma (PCG) is characterized by an isolated trabeculodysgenesis obstructing aqueous outflow without any other ocular or systemic anomalies.

**Incidence** PCG is a rare eye disorder which accounts for 0.01%-0.04% of total blindness. Its incidence varies from 1:10 000 to 1:20 000 in Western countries. PCG presents at birth or during early childhood (<3y) with 80% diagnosed before first birthday[10]. Various gene mutations with recessive pattern in 10%-40% cases (CYP1B1, MYOC and FOXC1) and consanguinity increase the risk of PCG[11].

**Clinical Manifestation** Classic presenting triad includes epiphora, photophobia and blepharospasm. Large eyeball size, hazy eyes or a red eye are less common presenting features. A thorough clinical evaluation including examination under anaesthesia may be required to confirm the presence of corneal enlargement, optic nerve head changes, buphthalmos and raised intraocular pressure (although it may be altered under anaesthesia).

**Management** Medical treatment including beta blockers, carbonic anhydrase inhibitors and prostaglandin analogues provide a supportive role only. The most effective primary surgical treatment is goniotomy, trabeculotomy or trabeculectomy. New techniques, including deep sclerectomy and viscocanalostomy appear promising. Refractory cases are managed by trabeculectomy with anti-fibrosis drugs, glaucoma drainage implants and cyclodestructive procedures[12]. Prognosis is affected by the age of glaucoma onset and its diagnosis, associated ocular defects and the treatment[13]. The worst prognosis is for patients presenting at birth or after one year of age. The future of PCG lies in possible development of a screening programme directed towards at-risk groups and research into best treatment options.

**CONGENITAL INFECTIONS**

**Toxoplasmosis**

**Incidence** The incidence of congenital toxoplasmosis per 10 000 live births significantly varies across geographical locations. In UK, incidence of symptomatic congenital toxoplasmosis was estimated in 0.34 per 10 000.

**Clinical manifestation** Ocular manifestations of congenital toxoplasmosis include chorioretinitis, optic atrophy and micropthalmia[14].

**Management** There are many treatment options, but the classical chemotherapy using pyrimethamine and sulfadiazine with corticosteroids continues to be the most widely used method[15].

**Rubella**

**Incidence** Since the introduction of the measles, mumps and rubella (MMR) vaccine in 1988, the incidence of congenital rubella syndrome has decreased significantly in UK. From 2005-2015, only 12 cases have been reported to the British Paediatric Surveillance Unit.

**Clinical manifestation** Ocular abnormalities in babies with rubella include congenital cataract (approximately 15%), micropthalmia, glaucoma, retinopathy, iris atrophy, keratitis and uveitis[16].

**Management** Because there is no cure for congenital rubella syndrome, infected babies are treated symptomatically. Hence, the best treatment is prevention (vaccination).

**Cytomegalovirus**

**Incidence** Cytomegalovirus (CMV) is the commonest congenital viral infection in the developed world, with an overall prevalence of approximately 0.6%[17].

**Clinical manifestation** Ophthalmic features of congenital CMV infection include chorioretinitis, cataract, microphthalmia, pigment retinopathy, strabismus and optic atrophy[18].

**Management** Treatment options include the use of potentially toxic drugs such as ganciclovir and valganciclovir which provide reduction in hearing loss and improvement in development of those treated at birth [19].

**Herpes Simplex Virus**

**Incidence** Incidence of neonatal herpes simplex virus (HSV) infection stands at approximately 1 in 3000-20 000 making it fairly uncommon, yet it is severe.

**Clinical manifestation** Congenital infection manifests principally as blepharoconjunctivits and keratitis[20].

**Management** Treatment involves high dose aciclovir and vigorous supportive therapy[21].

**Human Immunodeficiency Virus**

**Incidence** The risk of mother-to-baby human immunodeficiency virus (HIV) transmission has now significantly reduced to lower than 1% if the correct regime of treatment is followed[22].

**Clinical manifestation** Ophthalmic manifestations of HIV include opportunistic infections of the choroid and retina. Research into transgenic mice also found development of congenital nuclear cataracts, retinal microvasculopathy and uveitis. HIV infection was found to interfere with normal lens epithelial development in the embryo[23].

**Management** Best preventive strategy is early detection and treatment of mothers during pregnancy. If the baby is found to be infected postnatally, treatment requires highly active antiretroviral therapy.

**Varicella Zoster Virus**

**Incidence** Congenital varicella syndrome can occur in about 2% of babies following infection of the mother in first or second trimester[24].

**Clinical manifestation** It is characterised by cutaneous lesions, neurological defects, skeletal limb deformities and

ocular diseases. The latter includes cataract, micropthalmia, chorioretintis, and optic atrophy[25].

**Management** In order to prevent neonatal varicella, the newborn should be isolated from the mother until all maternal lesions have crusted and dried. When infection occurs in the period five days prior to, and two days after delivery, the newborn infant is at considerable risk for developing neonatal varicella. The infant should be treated immediately with Varicella Zoster Immunoglobulin +/- antiviral therapy (acyclovir)[26].

## ACQUIRED INFECTIONS

**Incidence** Ophthalmia neonatorum, a name given to neonatal conjunctivitis, is the most common infection occurring in up to 10% of neonates within the first month of life.

Babies can develop this if they are born to mothers who have contracted chlamydia, gonorrhoea or HSV. Some other organisms including staphylococci, streptococci, E. coli, pseudomonas, haemophilus influenzae and adenovirus can also cause ophthalmia neonatrum[27].

**Clinical Manifestation** Conjunctivitis can often be diagnosed clinically in the presence of typical symptoms such as gritty, sticky and watery eye with a red conjunctiva. In gonococcal infections, eyelid oedema and excessive discharge occurs. This clinical diagnosis can be confirmed by sending bacterial/viral and chlamydial conjunctival swabs.

**Management** Treatment depends on the cause and severity of the infection. Mild conjunctivitis typically requires a broad-spectrum antibiotic such as chloramphenicol or Fusidic acid in the form of a topical drop [28]. If the cause is chlamydial infection, oral erythromycin should be administered for a period of two weeks [29]. In gonococcal infections, treatment using a third generation cephalosporin should be started [30]. Treatment for HSV infection should be tackled systemically with intravenous (IV) acyclovir coupled with topical ophthalmic solution[31].

## CHILD ABUSE AND SHAKEN BABY SYNDROME

Shaken baby syndrome (SBS) is a form of physical abuse that occurs as the result of severe physical forces damaging the nervous system. Retinal hemorrhages are highly associated with abusive head trauma, particularly in children under age 6mo.

**Incidence** Increasing retinal haemorrhage severity is correlated with increasing likelihood of abuse [32]. Retinal haemorrhages are seen in up to 78% of abusive head trauma cases[33].

The pathogenesis of the ocular findings is the same as the intracranial manifestations, namely repetitive, to and fro acceleration-deceleration forces, that cause a displacement of vitreous volume and a resultant traction on the retina and retinal vessels resulting in rupture and haemorrhage.

**Clinical Manifestation** SBS manifests distinctively as a triad of cerebral damage, subdural/subarachnoid bleeding and retinal haemorrhage. Retinal haemorrhages in abusive head trauma are frequently bilateral, numerous and extensive [33]. Other ocular manifestations of SBS include blood-filled schisis cavities and circumlinear perimacular folds[34].

**Management** Surgical vitrectomy may rarely be needed for nonclearing vitreous haemorrhages, macular hole or retinal detachment. The prognosis can vary significantly for victims of SBS depending on the severity of trauma

## MICROPHTHALMOS AND ANOPHTHALMOS

Microphthalmos, defined as total axial length at two standard-deviations below similar age controls, is caused by disordered ocular intrauterine growth.

**Incidence** It occurs in around 1.2-1.8 in 10 000 births[35].

**Clinical manifestation** Microphthalmos (small eye) can be divided into two main classifications: total and partial. Nanophthalmos is a subtype of total microphthalmos. The distinction here is that both anterior and posterior segments are shortened along with enlarged lens and thickened sclera[36]. Anophthalmos is an extreme subtype of total microphthalmos, and is caused by early arrest in development or complete failure of optic vesicle budding resulting in total absence of one or both eyes. Anophthalmos can be associated with other abnormalities such as absence of extraocular muscles, short conjunctival sac and microblepharon.

**Management** In both micro and nanophthalmos, refractive errors should be immediately dealt with to prevent development of amblyopia. In microphthalmos and anophthalmos, associated chromosomal and midline brain abnormalities require further investigations such as magnetic resonance imaging (MRI) scan [37]. A small eye can cause problems later in life as an adult and this has implications especially in cataract, glaucoma and retinal detachment corrective surgery[38].

## COLOBOMA

Coloboma is defined as a defect or "hole" in the tissue formed during embryological development which can affect the eyelid, lens, iris, ciliary body, choroid or optic disc.

**Incidence** It is present in about 0.7 per 10 000 births [36]. Complex microphthalmos is often associated with coloboma.

**Clinical Manifestation** The effect of coloboma on vision depends where the coloboma is. A lid coloboma can be a feature of certain syndromes such as Treacher-Collins syndrome and Goldenhar syndrome. On the other hand, an iris coloboma may have other associations such as CHARGE (coloboma, heart defect, atresia of choanae, retardation of growth and development, genital hypoplasia and ear abnormalities) or syndromes such as Trisomy 13, trisomy 18, cat eye syndrome, klinefelter syndrome and Turner syndrome.

**Management** Treatment is aimed at managing associated abnormalities or syndrome. Glasses can be used to correct refractive errors, and sunglasses may be required due to light sensitivity.

## CRYPTOPHTHALMOS AND ANKYLOBLEPHARON

Complete cryptophthalmos presents at birth with the eyelid skin completely covering the eye while in incomplete/partial cryptophthalmos, eyelid skin fuses with the conjunctiva or cornea. Occasionally, bilateral cryptophthalmos can be associated with Fraser syndrome [39]. Underlying ocular structures are usually malformed and cosmetic surgical repair has guarded prognosis. On the other hand, ankyloblepharon is usually an isolated abnormality, characterised by an adhesion of the edges of the upper and lower eyelids. Underlying eye is usually normal and prognosis is excellent with a relatively simple excision of adhesions connecting the eyelids[40].

**Entropion and Epiblepharon** In-turning of the eyelashes at birth is either due to inversion of the eyelid margin (entropion) or secondary to an abnormal fold of skin that overrides a normally positioned eyelid margin (epiblepharon). Congenital entropion usually requires early surgical correction [41] while epiblepharon rarely requires surgery and resolves over time[42].

**Dacryocystocoele** Congenital dacryocystocoele is lacrimal sac distension presenting as a cystic bluish swelling just inferior to the medial canthus at birth. As it carries high risk of infection, an early referral for surgical probing and decompression is warranted [43]. Infected dacrocystocoele requires systemic antibiotic therapy.

**Aniridia** Aniridia is hypoplasia or absence of iris and usually involves both eyes. It is often associated with other ocular abnormalities, including macular/optic nerve hypoplasia, cataracts, glaucoma and corneal opacification leading to reduced vision and nystagmus[44]. About two-thirds of affected patients have familial aniridia with autosomal dominance inheritance. It is important to identify patients with sporadic aniridia as they have significantly increased risk (30%) of developing Wilms tumour[45]. All patients with sporadic aniridia should be regularly screened with serial abdominal ultrasound scans for early detection of Wilm's tumour. Treatment may require frequent use of lubricants, opaque contact lenses to create an artificial pupil and cataract surgery.

**Ptosis** Congenital ptosis refers to vertical narrowing of the palpebral fissure secondary to drooping of the upper eyelid to a lower than normal position from birth. It is generally sporadic and unilateral (70%) [46]. It is usually caused by developmental dysgenesis of levator palpebrae superiorus muscle. Bilateral ptosis may be associated with blepharophimosis syndrome.

**Clinical manifestation** Neurological causes include Horner's syndrome resulting from injury to sympathetic pathway (ipsilateral ptosis, miosis and anhidrosis), oculomotor nerve palsy (resulting in down and out position of the affected eye) and Marcus Gunn jaw winking syndrome (ptosis and excursion of the ptotic upper eyelid when the infant is chewing or sucking). Mechanical causes of ptosis (eyelid masses) can easily be excluded by careful inspection and palpation of eyelid.

**Management** Ptosis can induce significant astigmatism resulting in amblyopia. Surgical correction may be carried out if there is significant interference with the visual field (lid drooping over the pupil) to prevent amblyopia development. Surgical techniques include traditional frontalis sling, levator resection and advancement, Whitnall sling procedure, frontalis muscle flap and mullerectomy[47].

## RETINOPATHY OF PREMATURITY

Retinopathy of prematurity (ROP) results from disordered retinal vascular development in preterm infants and remains a major preventable cause of visual impairment.

**Incidence** ROP remains one of the more common forms of childhood blindness, worldwide and accounts for around 3% of all childhood vision loss [48]. Birth weight and gestational age are most important risk factors for ROP [49]. Other risk factors include early exposure to high levels of oxygen, anaemia, sepsis, intraventricular haemorrhage and mechanical ventilation.

**Screening** Screening and treatment of at risk infants prevents the progression and thus reduces the risk of visual loss. In the UK, joint guideline from British Association of Perinatal Medicine, BLISS, Royal College of Paediatrics and Child Health and Royal College of Ophthalmologists have recommended screening for all infants born <32wk gestation or with a birth weight <1501 g prior to discharge from the neonatal unit [50]. ROP screening should be undertaken at 30-31wk post menstrual age for babies born before 27wk gestational age. Babies born at/after 27wk gestational age have their ROP screening performed at 4-5wk of postnatal age. Further screening is stopped when the baby is no longer at risk of sight threatening ROP.

ROP is classified into 5 categories ranging from mild (stage I) to severe *i.e.* stage IV and V denoting partial and complete retinal detachment respectively.

**Management** Treatment depends upon ROP progression. Conventional treatment involves laser retinal photocoagulation, under sedation or general anaesthesia. Other treatment options include vitreoretinal surgery for severe ROP and intravitreal injections of anti-vascular endothelial growth factor preparations as salvage therapy although its safety and efficacy has not yet been established[51-52].

**Retinoblastoma** Retinoblastoma is the most common neural retinal intraocular malignancy of childhood.

**Incidence** It accounts for 3% of all childhood cancers. It is a very rare tumour with an estimated 40-50 children diagnosed in the UK per year[53]. Most cases present in children <5y with peak incidence under 1 year of age.

Non-heritable (somatic) retinoblastomas make up 60% of cases. The other 40% are heritable (autosomal dominant),

caused by a mutation in the retinoblastoma (Rb1) gene found on long arm of chromosome 13 which codes for an important tumour suppressor protein. Genetically inherited retinoblastomas typically, but not always, present bilaterally contrary to de novo mutations which tend to be unilateral. These sporadic mutations also usually affect children at a slightly later age than the inherited form.

**Clinical manifestation** Most common sign of retinoblastoma include a white reflex (leukocoria) instead of a normal red reflex or complete absence of the red reflex where the eye may just look black. Other signs include strabismus (squint), heterochromia (change in iris colour), an unexplained painful/red eye or orbital cellulitis [54]. If Rb1 mutation is identified on genetic testing, it is important to refer the family for genetic counselling.

**Management** Retinoblastoma has an extremely low mortality rate achieving long term cure from the disease with an estimated 99% ten year survival rate [55]. The choice of treatment depends upon the stage of the tumour, whether one or both eyes are affected and the potential for vision. It ranges from local therapy (indirect laser trans-pupillary thermotherapy, trans-scleral cryotherapy and indirect laser photocoagulation), enucleation, photocoagulation laser, external beam therapy (EBR), radiotherapy and chemotherapy[53].

**VISUAL IMPAIRMENT AND AMBLYOPIA**

Visual acuity is estimated to be approximately 20/400 at birth and the ability to fixate only develops at around 6 weeks of age. Cortical visual impairment, due to hypoxic-ischaemic insult, is the most common cause of bilateral vision loss at birth in the developed world. Visual impairment and neurological deficits corresponding to the area of injury may not be recognised early especially in premature infants.

**Incidence** Amblyopia is diminished vision due to abnormal visual stimulation early in life and it is one of the leading causes of monocular blindness [56]. It affects approximately three per cent of the population and carries a projected lifetime risk of visual loss of at least 1.2%.

Amblyopia can be unilateral or bilateral and results from any condition that prevents the eye from focusing clearly. First few months of life are critical for visual development. Any obstruction to the visual pathway during this time such as untreated cataract will result in poor visual input leading to severe degree of amblyopia. Later in childhood, strabismus and anisometropia (asymmetric refraction between the two eyes) can also lead to amblyopia. Other causes include high myopia or hyperopic refractive errors, media opacities, retinal disease, optic nerve pathology and corneal disease.

**Clinical manifestation** Pupillary reaction to light and blink to light response in both eyes remains the most useful test of visual function at birth [57]. Early-onset nystagmus and lack of pupillary constriction or a behavioural response to a bright light may also indicate visual impairment.

**Management** The key to optimal treatment is early detection and intervention. The quicker amblyopia is detected and addressed the less negative effect it has on the visual system. Occlusion of the normal eye, to encourage use of the amblyopic eye, is the most effective treatment. An alternative method is penalization (atropine to blur the vision in the normal eye) which is used if compliance to occlusion is poor.

**NYSTAGMUS**

Nystagmus is repetitive, involuntary, to-and-fro oscillation of the eyes. It can be symmetric *vs* asymmetric, unilateral *vs* bilateral and conjugate (both eyes move together) *vs* disconjugate.

**Clinical Manifestation** In congenital idiopathic nystagmus, infants develop nystagmus in all positions of gaze but with clinically normal eyes and normal developmental milestones. This diagnosis is only made when other neurological and ocular abnormalities have been excluded. Neurological nystagmus can be associated with space occupying lesions, metabolic diseases and neurodegenerative disorders. Sensory deprivation nystagmus occurs as a result of an abnormality at some point in the visual pathway, leading to sensory deprivation. It accounts for 80%-90% of childhood nystagmus and is common in ocular conditions with poor vision. This includes corneal opacities, aniridia, albinism, ROP, achromatopsia (non-progressive hereditary visual disorder characterized by decreased vision, light sensitivity and the absence of colour vision) Leber's congenital amaurosis and optic nerve abnormalities[58].

**Management** Treatment depends upon the aetiology of nystagmus. Surgery for nystagmus may be considered if there is an abnormal head posture with a null position (position of the head that results in the slowest movement of the eyes) or for congenital motor/sensory nystagmus without a null point.

**SQUINT (STRABISMUS)**

Strabismus or squint develops where the eyes do not look in the same direction.

**Clinical Manifestation** Approximately 2/3 of all infants have exotropia (outward deviation of the eyes) at birth. Vast majority of transient strabismus noticed at or soon after birth are comitant (angle of deviation remains the same in all fields of gaze) and resolve by 6 months of age.

Strabismus is rarely seen in congenital fibrosis of the extraocular muscles which is a rare non-progressive disorder characterised by bilateral ptosis and paralysis of the ocular muscles. Vertical movements of the eye are always restricted significantly but horizontal movement can vary from none to normal.

Duane syndrome is a congenital and non-progressive type of strabismus characterized by difficulty in abduction or adduction of the eye as a result of 6$^{th}$ cranial nerve which does not develop properly. There is also irregular innervation to medial rectus from a branch of 3$^{rd}$ cranial nerve.

Möbius syndrome is a rare congenital neurological disorder which is characterized by facial paralysis and the inability to move the eyes from side to side due to underdevelopment of VI and VII cranial nerves.

**Management** Any incomitant strabismus that persists beyond 3-6 months of age should warrant a referral to an ophthalmologist to prevent amblyopia [59]. Treatment options include prescription glasses, occlusion therapy (patching), exercises, surgery or botox injections.

## CONCLUSION

There is a wide range of congenital and acquired eye disorders affecting a neonate. A significant number of these conditions have signs that are detectable on a screening eye examination. Good history and comprehensive newborn examination are key components to early detection and intervention. Prior knowledge and awareness of specific signs of these ocular disorders are vital constituents to achieve a meaningful outcome at an early stage. Hence, authors would recommend NIPE (including screening eye examination) within 24-72h after birth for all newborn babies across the globe. Appropriate training and assessment of those undertaking NIPE is fundamental to its success. Further assessment by family physician or general practitioner at 6 weeks of age is likely to further enhance the detection rate.

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