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**Chapter**

# Congenital Nasolacrimal Duct Obstruction and the Visual System

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## Abstract

Congenital nasolacrimal duct obstruction (CNLDO), previously considered a benign disease, affects 20% of the children globally. It is described by a collection of symptoms in which continuous epiphora and intermittent discharge are present in either one or both the eyes. CNLDO usually resolves in most healthy infants in the first few couple of months; however, it may persist for a number of years in some children. There has been a lot of recent deliberation on how a constant watery eye affects the visual development during the phase of emmetropization in children. A connection between CNLDO and anisometropia has been hypothesized. Multiple factors which include developmental and environmental aspects are thought to play a contributory role in the development of anisometropia by and large; particularly hypermetropic anisometropia, raising the chances of developing amblyopia in children with CNLDO. Published literature on CNLDO had shown inconclusive evidence on this anecdotal propinquity. This chapter discusses CNLDO; etiology, pathogenesis, treatment modalities, surgical intervention, and its role in inducing refractive errors; and its propensity to cause amblyopia.

**Keywords:** congenital nasolacrimal duct obstruction, anisometropia, refractive status, amblyopia

## 1. Introduction

Tears are words that need to be written (*Paulo Coelho*). Tears physiology and fluid dynamic are intricate and multifaceted. Tears are produced by the main and accessory lacrimal glands and drain medially into the puncta, then flow through the canaliculi to the lacrimal sac, and then through the nasolacrimal duct (NLD) into the nose. Contraction of the orbicularis muscles creates a pumping action that facilitates the flow of tears through the lacrimal system. Congenital nasolacrimal duct obstructions (CNLDO) are one of the most common cases seen in pediatric ophthalmology clinics. CNLDO occurs in 5–15% of full-term newborns [1]. CNLDO is characterized by epiphora and intermittent discharge. CNLDO remains the most common cause of epiphora in infants. It is usually unilateral or asymmetric and is largely due to a persistent membrane at the level of Hasner valve. The valve of Hasner is located at the distal end of the nasolacrimal duct where it enters the inferior meatus lateral to the inferior turbinate.

The valve of Hasner obstruction occurs due to unfinished canalization, a process that begins in the 12th week of gestation and is completed by the 24th week. An incidence of 35–73% has been reported for imperforate NLDs in full-term infants,

with a preponderance opening up spontaneously during the first couple of weeks of life [2]. The nasolacrimal duct normally canalizes from proximal to distal, so the distal portion is often last to open up. Therefore, premature infants conceivably have higher rates of CNLDO. However, because tear production does not take place almost near term, these infants mostly do not exhibit the symptoms of epiphora. Infants with CNLDO present with excessive tearing or mucoid discharge from the eyes due to blockage of the nasolacrimal duct system, which can result in maceration of the of the eyelid skin and local infections. On examination, there is an increased tear meniscus and there may be stickiness or crusting on the lashes. Secondary infection is common in CNLDO due to the stasis of lacrimal sac contents, proximity of the sinuses, and a rich lymphatic and vascular system within the submucosa of the lacrimal sac.

## 2. Initial assessment

It is important to note that typically, CNLDO does not usually cause much discomfort to children. Affected infants are otherwise well and act normally despite the presence of noteworthy overflow of tears and mucopurulent discharge. If infants have photophobia or other signs of chronic irritation, they should be checked carefully for signs of glaucoma, keratopathy, or epiblepharon, i.e., other factors of pediatric epiphora must be ruled out. The absence of corneal and conjunctival abnormalities is an important factor in establishing a diagnosis of CNLDO. Other causes of epiphora such as acute conjunctivitis, congenital anomalies of the upper lacrimal drainage system (punctal or canalicular atresia or agenesis), entropion, and triachiasis also must be evaluated. The most important entity in the differential diagnosis of CNLDO/epiphora would be infantile glaucoma. NLDO may be confused with glaucoma by primary care physicians due to the presence of epiphora. It is important to check intraocular pressure, corneal diameters, and cup to disk ratio to rule out this condition.

It is recommended to do a fluorescein disappearance test (FDT) on all children with epiphora as it provides evidence to support a diagnosis of lacrimal outflow obstruction. Fluorescein 1% is instilled into each lower conjunctival fornix. The child sits on the parent's lap while the cobalt blue light of a slit lamp is used to illuminates the eyes. Cobalt blue light of an ophthalmoscope can be alternatively used. The tear meniscus is evaluated at 2, 5, and 10 minutes. Each eye is graded at 0, 1, 2, or 3 (0 = fluorescein completely gone, 3 = no fluorescein gone). Normally, the fluorescein disappears by 5 minutes but the dye remains in the conjunctival cul-de-sac in children with obstruction. Mild pressure on the lacrimal sac produces regurgitation of fluorescein-stained tears, particularly in those with a mucocele. This test visibly demonstrates the nature of the problem to the parents and provides practical time to discuss the cause and management of CNLDO. The fluorescein dye disappearance test can reliably confirm lacrimal duct obstruction noninvasively, with a sensitivity of 90% and a specificity of 100% [3]. In most centers, FDT has become the preferred tool for diagnosis of CNLDO.

Approximately 90% infants with CNLDO experience spontaneous resolution before the age of 1 year. It becomes symptomatic in merely 5–6% of infants [4]. Probabilities of spontaneous resolution by 12 months of age are 80–90%, at 3 months of age, 68–75%, at 6 months of age, and 36–57% at 9 months of age [5]. Bilateral symptoms are present in 14.0–33.8% of patients with CNLDO, all of which either spontaneously resolve simultaneously or within 3 months of contralateral resolutions. In cases of bilateral CNLDO, when epiphora in one eye settles spontaneously during 10–12 months of ages, it is rational to monitor the

child for further 3 months as spontaneous resolution can occur in a substantial percentage of children after 1 year of age [6].

Congenital dacryocystoceles are an uncommon variant of CNLDO, typically seen at birth or shortly after birth as a blue-colored cystic mass over the lacrimal sac. The valve of Hasner again is the most frequent site obstruction due to incomplete canalization. A congenital dacryocystocele accompanies CNLDO in approximately 0.1% of infants. Children with Down syndrome, craniosynostosis, Goldenhar sequence, clefting syndromes, hemifacial microsomia, and midline facial anomalies are at an increased risk for CNLDOs. Although most cases of CNLDO are diagnosed clinically, some conditions especially craniofacial malformations or Down syndrome, the bony obstruction at the CNLDO can be confirmed with computed tomography (CT Scans). Dacryocystocele (where both proximal and distal lacrimal system are obstructed) commonly results in dacryocystitis (or, rarely, neonatal respiratory obstruction) at birth, it necessitates surgical intervention following diagnostic imaging.

## 3. Initial Management

The treatment of CNLDO is, at first, conservative. Conservative treatment consists of nasolacrimal massage, warm compresses, and topical antibiotics for secondary infections. Massage of the lacrimal sac increases the hydrostatic pressure within the sac thereby breaking open the distal membrane. The most important aspect of conservative treatment is educating the parents, providing reassurance and information about the etiology, and natural history of CNLDO. Printed leaflets that provide information for the parent are very useful. Parents should be encouraged to clean the lids and lashes with cooled boiled water or normal saline and to lightly express the contents of the lacrimal sac. This maintains flow in the system and prevents stagnation, reducing any sticky discharge. Method of the massage should be explained to the parents. Parents find this difficult and need clear instructions. They should press on the sac below the medial canthus with their little finger multiple times per day if possible. Vaseline or liquid paraffin should be applied to the periocular skin to protect and treat any areas of redness or broken skin.

Antibiotic eye drops in CNLDO should only be used when it is accompanied by signs of conjunctivitis. It is somewhat common practice in some centers that topical antibiotics are used in combination with conservative therapy for CNLDO. However, there is no evidence indicative of the fact that antibiotic eye drops appreciably facilitates the resolution of CNLDO. Conjunctival bacterial flora in CNLDO patients is almost identical to those in the normal pediatric population and the use of antibiotic eye drops may cause normal bacterial flora to be substituted with a drug resistant flora. As infants have immune system that is in flux and is not geared-up to remove resistant bacteria they may possibly become carriers of resistant bacteria. Thus, antibiotic eye drops are completely unnecessary in conservative therapy for simple CNLDO [7].

### 3.1 Surgical management

Intervention is usually done when CNLDO becomes persistent and/or once the child is older than 1 year of age. Probing the nasolacrimal duct to open the membranous obstruction at the distal nasolacrimal duct is the preferred initial management. Probing can be performed without anesthesia in the office setting, but it is usually preferred to do the procedure under general anesthesia (GA) in the operating room. The benefit of GA is less discomfort and the ability to perform

additional procedures if other abnormalities are found while the child is under GA. Probing aims to solve the symptoms of epiphora/discharge by clearing up the membranous obstruction; however, it may not be able to relieve the obstruction if it is due to protrusion of the bone of inferior turbinate into the NLD or when the NLD is swollen due to inflammatory processes such as dacryocystitis. Moreover, probable complications with probing are; false passage formation, injury to the NLD, puncta, canaliculi, bleeding, laryngospasm, and rarely aspiration.

While obstruction is mostly located at the valve of Hasner, obstruction may be anywhere along the route. Surgical intervention consists of the introduction of a flexible metal probe into the nasolacrimal duct to open it. A probe is placed into the nasolacrimal duct and passed into the nose. Following probing the nasolacrimal system is irrigated to assess its patency. This is usually done with normal saline tagged with fluorescein dye. If fluorescein dye can be picked-up by suction from the pharynx, probing can be considered successful. Postoperative tobramycin-dexamethasone eye drops are used four times a day for 2–3 weeks. If after 6 weeks, there is no improvement in signs or symptoms, probing and syringing (P&S) can be repeated. Endoscopic inspection with a nasal scope during P&S is recommended; especially if it is being done the second time, to identify anatomical anomalies and to ensure accurate probe configuration. Various studies show a success rate of 90–95% after initial probing [8–11].

The timing of initial probing is debatable and varies between surgeons and centers. Some surgeons recommend early intervention. Their concern is that prolonged epiphora is annoying to both child and parents. More importantly, a delay in treatment may increase the risk of infections and long-term damage to the system resulting in inferior success rates of simple probing. In countries where pediatric ophthalmic care is limited to a few urban centers; where children present late with complex CNLDO and where there is a high probability the child will not show up for a follow-up, an early probing can be justified to some extent.

Typically, it is thought that the older the child at the time of probing, the less successful the probing will be. Studies have reported variable success rates of probing and syringing when done in older children. A success rate of 94% was reported by Havins and Wilkins for probing done in children less than 8 months compared to 56% in children age 18 months and older [12]. Sturrock reported 86% success when probing was done in children less than 1 year compared to 72% between 1 and 2 years of age and 42% for more than 2 years of age [13]. Katowitz and Welsh reported success rates of 76.4% in 13–18 month old children; however, the cure rates fall to 33.3% in children over 2 years [9].

Mannor et al. found a negative association between the age and success rates of P & S. Contrary to this, Robb, Zwaan, and El-Mansoury found more than 90% success rate in late as well as very late probing [10, 14, 15]. Robb found no difference in cure rate with increasing age and noted an overall success rate of 92% varying from 88.9 to 96.8% at different age intervals up to and beyond 3 years of age [16]. Honavar reported a success rate of 75.0% up to 4 years of age, after which it fell to 42.9% in children older than 4 years [17]. Casady reported success rates of 85% for probing in children more than 18 months of age [18].

Factors besides increasing patient age that are associated with decreased success rates for probing are severe symptoms, bilateral symptoms, canalicular stenosis, atonic sac, and non-membranous CNLDO. A recent Cochrane review assessing the effects of probing for CNLDO showed that the effects and cost of immediate versus deferred P & S for CNLDO are uncertain. Patients with unilateral CNLDO may have improved success from immediate P & S in the clinic. Limiting factors in these studies were; sample sizes of participated children in these trials were small and researchers examined outcomes at different points in

time. They conclude that deciding whether to perform the procedure and its best possible timing will entail well-run clinical trials [19].

If the preliminary probing and syringing fails, one may perform; as discussed before, a secondary probing or an additional procedure. Second probing can be repeated four to six after the initial procedure. Cure rates of second probing are greatly decreased because unsuccessful first probing can result in cicatricial strictures or a false passage [20]. The two main secondary procedures are balloon dacryoplasty and silicone tube intubation.

During balloon dacryoplasty, a stent with a balloon at its distal end is passed into the distal nares, the balloon is inflated (usually couple of times), then deflated and removed. The aim is to widen the distal duct and decrease obstruction. The primary advantage of balloon dacryoplasty is that no stent material is left in the lacrimal system and therefore stent removal is not required. Balloon dacryoplasty is particularly useful for patients with diffuse stenosis of the distal NLD. Success rates for balloon dacryoplasty as a primary procedure are as high as 94%; however, the procedure is costly; nevertheless it may have its benefit in intractable cases [21, 22]. Furthermore, the role of balloon dacryoplasty in the management of CNLDO needs further evaluation and assessment.

Intubation is necessary in cases with lacrimal canalicular stenosis after probing. The silicone tube prevents the formation of granulation-related obstruction around the newly patent tract. Bicanalicular or monocanalicular silicone intubation of the nasolacrimal duct can be used as a primary or secondary procedure. Intubation should take place under GA after the nose has been prepared with decongestant. It is recommended that a nasal endoscopic guidance system is used to view the inferior meatus [23]. The lacrimal system should be probed first to ensure that the tubes have an anatomical passage. Tubes come with a metal introducer and one end should be placed through the system via the upper canaliculus, into the sac and down the nasolacrimal duct into the inferior meatus from where it should be retrieved under endoscopic view. The other end of the tube is inserted in exactly the same way through the lower canaliculus. The ends are tied securely with multiple square knots inside the nose and trimmed. Postoperative treatment consists of a topical antibiotic and steroid preparation for 2–3 weeks.

Possible complications of intubation include canalicular cheese-wiring, superiorly/inferiorly dislocation, infection, and scarring of any part of the nasolacrimal drainage system. Silicone tube stents if removed too early may result in the recurrence of obstruction. Breakage or prolapse of the tube may cause corneal abrasions [24]. Retrieval of the probe is sometimes difficult during intubation and during instrumental manipulation required during it may damage the nasal mucosa and turbinate [25]. The timing of removing the tube is contentious, but the suggested time is anywhere between 6 weeks and 18 months [26]. Leaving a tube in situ for about 6 months may attain better success rates compared to removing it earlier [27]. A study reports that early removal of tube in children younger than 2 years did not reduce the success rates of intubation [28]. Long-term intubation is associated with a higher occurrence of breakage, dislodgement, migration, dislocation, or prolapse. Tubes in almost all the cases are removed under GA through the nose. The tube is cut at the medial canthus and removed under direct vision to prevent aspiration of the tube. This system is then irrigated to remove any debris and to verify patency.

Its success rate of intubation range from 62 to 100% but in general, they decrease with increasing age [29, 30]. A study reported success rates for intubation stratified by patient age. The success rate for intubation in children aged 12–24 months was 91.3%, which reduced to 85.5% in those aged 24–36 months and to 79.6% in those aged 36–48 months [31]. Several studies have explored the effectiveness of intubation as a main treatment modality in older subgroup of children because of the

decrease in success rates for late probing. Although the success rate was high; none of the studies included a control group.

The bicanalicular device has a silicone tube with a flexible metal probe on each end. Each separate end is introduced into the upper or lower punctum and then retrieved from the nose. Bicanalicular stents pass through both the upper and lower canaliculus and typically create a closed circuit. Bicanacular system intubates the upper and lower canaliculi connecting via the common canaliculus or the lacrimal sac thereby intubating the entire nasolacrimal drainage system with the circuit being open or closed in the nose. Examples of Bicanacular stent include Crawford stent, Ritleng stent, Pigtail/Donut stent, and Kaneka Lacriflow stent.

Monocanalicular stents do not provide a closed loop system, but only intubates either the upper or lower canaliculus. Examples of monocanalicular stents include Monoka Stent and Jones Tube. Both monocanalicular and bicanalicular intubations are effective methods for treating CNLDO. Monocanalicular intubation has the advantage of a lower incidence of canalicular slit formation, technical ease of insertion, and easier tube removal. Moreover, the tubing does not threaten the un-probed part of the lacrimal drainage system [32]. Bicanalicular intubations may be a better treatment for the patients with incomplete complex CNLDO [33].

A met-analysis in 2016 showed that the results of immediate and deferred P & S did not vary in their success rates. There was no difference in between the success rates of balloon dilation and intubation. Monocanalicular and bicanalicular intubation had similar success and dislocation rates. Therefore, the preference of a particular procedure on the treatment of CNLDO should be discussed in detail with parents by the concerned surgeon to achieve the best possible results [34].

In cases where all above measures fail or in complex CNLDO, some surgeons perform additional procedures such as turbinate fracture or dacryocystorhinostomy (DCR). DCR is done provided the obstruction is distal to the lacrimal sac. DCR represents a last resort for patients in whom; multiple procedures have failed, complex CNLDO, or in whom there is obstruction secondary to bony obstruction, dacryocystitis, dacryocystocele, older children, or craniofacial dysmorphism. Infracture of the inferior turbinate, usually done with a periosteal elevator or a hemostat, is used to decrease the resistance of drainage in the distal nasolacrimal duct. It is mostly useful for patients who have an exceedingly tight space between the inferior turbinate and nasal wall. It also allows for better visualization of the inferior meatus during endoscopic surgery. The success rate of inferior turbinate fracture alone is 83% [35]. Although a combination of probing with intubation results in good cure rates of 88–100%, the success rate for a combined inferior turbinate fracture and probing is no different to that for simple probing [36].

Conventional/external DCR is carried out through skin incision, the lacrimal sacs are exposed, an osteotomy is made through the nasal bone, flaps are created between the lacrimal sac and the nasal mucosa and then tube is placed which serves as a stent. Laser DCR is a substitute; the ostium is created by means of a laser which is placed through the canaliculus just adjacent to the nasal bone. An endoscope is mostly used during laser DCR. Nasolacrimal stents are placed at the end of the procedure. External and endoscopic DCR have excellent success rates, comparable to those of adult DCRs [37]. Endoscopic DCR can avoid a cutaneous scar and disruption of the medial canthal anatomy, but a pediatric endoscopic DCR is technically more demanding because of the poor visualization afforded by small nostrils and closer proximity of the operative field to the base of the skull [38].

Pediatric DCR has high success rates of 88–96% for external DCR and 82–92% for endoscopic DCR [39]. Rapidly altering anatomy, ill-defined anatomical landmarks, and aggravated growth of scar tissue have been suggested as possible factors that could influence surgical outcomes in pediatric DCR. On top, because of a

narrowed nasal cavity there is a propensity toward development of postoperative adhesions between the rhinostomy site and the nasal septum; the use of a silicone tubes in pediatric DCR may avert this obstruction and consequently ensure better surgical outcomes [40].

## 4. CNLDO and its effect on the visual system

CNLDO has long been considered as a benign condition that does not influence visual development. CNLDO has been at the hub of current debate on its proposed relationship with anisometropia, strabismus, and amblyopia. The persistent tearing caused by CNLDO distorts retinal images by producing a blur, thus defocusing the retinal image thereby adversely influencing the process of physiological emmetropization. This interference with the physiological emmetropization has possibly led to frequent findings of anisometropia in various studies.

The role of focused retinal images in the physiological emmetropization has been discussed by Wright [41]. Newborns are hyperopic having a short axial length relative to the refractive power of the cornea and lens. During the first few months of life rapid growth in axial length (AL) occurs with subsequently decreases the hypermetropia. The retinal image comes in clear focus through "emmetropization." Various studies have shown that growth of the eye after birth and the development of its refractive capabilities are dependent on vision-dependent retinal mechanisms. A basic observation is that a continuous image blur on the retinal cells in a new born can result in lengthening of the axial length thus inducing myopia. The axiom is that when we are born the AL of the eye is short; therefore, the eye is hypermetropic and image blur on the retinal tissue in early life kindles AL elongation until image clarity is achieved by proper focusing of light rays. Raviola and Wiesel concluded that when visual input is deprived, as seen in cases where there is a dense corneal opacity or ptotic/closed eyelids, the eye has a tendency toward myopia [42]. Even if the eyelids are completely closed, more than 20% of light is still passed on to the retina [43]. The influence of a blur images is so immense that (in a study done on chicks) if only half the retinal image is blurred, then only that half of the globe will lengthen [44].

In comparison to blurred images, if there is no stimulation of light, studies show that it slows down the progress of blurred induced myopia and AL elongation. In theory, clearing up the image blur would abolish the stimulus of image blur on AL elongation, thereby retarding AL growth and the process of emmetropization, thereby causing hypermetropia [45]. In addition to the influence of AL elongation by blurred image stimulation of the retina, it seems that intrinsic growth of the eye is disengaged from visual input. AL elongation and thickness of the choroid alterations occur in diurnal pattern. In general, AL elongates and choroid thickens during the day and dawdle downs at night signifying a circadian rhythm. This suggests that the eye has an intrinsic growth rate that will occur in the absence of visual input [46].

No cause-effect relationship linking CNLDO and anisometropia has been studied and the precise method by which CNLDO might cause refractive error, anisometropia, and amblyopia is indistinct. As discussed, the proper focusing of images on the retina early in life is vital for emmetropization. It is indefinite what part, if any; persistent tearing has on visual development, refractive status, and amblyopia. Several authors have recently described an association between CNLDO and the development of amblyopia and strabismus secondary to anisometropia [47–49]. The major visual concern in CNLDO is the presence of significant anisometropia during vital period of visual development in these infants.

CNLDO rarely, if ever, results in complete visual obstruction. Besides, early unilateral visual deprivation as discussed before has been linked with myopia not hypermetropia [42, 50]. It is postulated that accumulation of discharge, excessive tears, and antibiotic ointments may result in deformation of retinal images. This image disparity may lead to a lack of appropriate emmetropization process and as a result the repeated finding of anisometropia in the affected eye. It is also proposed that this anisometropia is refractory. However, recent studies reveal that this is not necessarily true [51], which will be discussed in a while.

**4.1 Visual system, anisometropia, and amblyopia**

An estimated 285 million people around the world are visually impaired; 19 million are children below the age of 14 years. Childhood visual impairment is estimated to be the second leading cause of the burden due to blindness [52]. Forty percent of childhood blindness is preventable; 12 million children are visually impaired merely because of refractive errors. Uncorrected refractive errors lead to amblyopia and strabismus [53, 54]. Anisometropia is one of the major causes of amblyopia. Visual disabilities in children are also more intricate compared to adults thus preventing visual impairment in children in resource-poor countries is one of the key components of VISION 2020 the Right to Sight.

The significance of anisometropia as a source of amblyopia is well documented. Amblyopia risk factors based on *American Association for Pediatric Ophthalmology and Strabismus* (AAPOS) criteria include: anisometropia (spherical or cylindrical) >1.5 diopters; any manifest strabismus; hypermetropia >3.5 diopters in any meridian: myopia magnitude >3.0 diopters in any meridian: any media opacity >1 mm; astigmatism >1.5 diopters at 90 or 180° >1.0 diopters in oblique axis (more than 10° from 90 or 180°) and ptosis ≤1 mm margin reflex distance (MRD) [55]. Although binocular single vision (BSV) develops at the age of 2 years, the fixation reflex is not fully established until the age of 9 years. Visual acuity remains in a state of flux prior to this age predisposing the child to anisometropia, strabismus, and amblyopia. In a population-based study on 961 children with amblyopia, the author found the cause to be strabismus in 57%, anisometropia in 17%, and combination of two in 27% patients [56].

Donahue suggests that 1D of anisometropia can be considered as clinically significant anisometropia [57]. Nevertheless due to individual physiologic variability's, amblyopia can even be seen with milder degree of anisometropia. The prevalence of anisometropia in the general pediatric population ranges from 2.3 to 3.4%, based on literature review [58]. Amblyopia has been reported to occur in approximately 1.6–3.6% of the normal population [51, 58]. The prevalence is even higher in medically underserved populations with reported rate as high as 22.7% [59]. The population-based Multi-ethnic Pediatric Eye Disease Study found that 78% of African American and Hispanic children had amblyopia which was traced back to be due to anisometropia [60]. A population-based Baltimore Pediatric Eye Disease Study was conducted on the White and African-American Children. This study concluded that 32% of cases of amblyopia were attributed to anisometropia [61].

Studies on the prevalence of anisometropia (greater and equal to 1D between two eyes) reveal that 2.3–3.4% of pediatric population aged 5–11 years is affected [62, 63]. Drover et al. showed the prevalence of anisometropia to be at 1.4% in the studied pediatric population (mean age 4.2 years) [64]. Huynh et al. study conducted in Sydney, concluded an anisometropic prevalence of 1.6–2.4% (mean age 6.7 years) [65]. Shih and colleagues conducted a population survey in Taiwan and found an anisometropic prevalence ranging from 7.2 to 9.3% in older children (age, 7–18 years) [66]. Studies show that anisometropia is an identifiable amblyogenic

factor in 37% of cases and present concurrently with strabismus in an additional 24% of clinical populations [67].

Apart from refractive errors, a variety of risk factors increase the likelihood of amblyopia. A study showed that 28.7% of children whose parents had known strabismus were also found to have strabismus, a known amblyopia risk factor; this suggests a hereditary risk factor [68]. Low birth weight (<2499 g) and severe mental handicap are established risk for developing amblyopia [69]. Further risk factors include capillary hemangiomas of the eyelids, ptosis, blepharophimosis, craniosynostosis, and hydrocephalus. Socioeconomic factors also increase the risk of developing amblyopia. Children from underprivileged background, such as homeless kids and those coming from homes where either parents smoke, have a high prevalence of amblyopia [70, 71].

Amblyopia is clinically significant because it is one of the main causes of visual loss in children. Amblyopia is also of central interest because it suggestive of diminished neuronal activity that occurs when normal visual growth is interrupted. Amblyopia affords an idyllic template for understanding when and how a plastic brain may be used for functional recovery. Impaired stereoscopic depth perception is the most common deficit associated with amblyopia under ordinary binocular viewing conditions. This impairment may have a substantial impact on visuomotor tasks and difficulties in playing sports in children. Furthermore, impaired stereopsis may also limit career options for amblyopes. Stereopsis is more affected in strabismic than in anisometropic amblyopia. Recovery of stereoacuity may require more vigorous treatment protocols in strabismic than in anisometropic amblyopia. Individuals with strabismic amblyopia have a very low probability of improvement with monocular training; however, they get on well with dichoptic training (promising new therapeutic approach to amblyopia, which employs simultaneous and separate stimulation of both eyes) than with monocular training and much better with direct stereo-training [72, 73].

Thus, Anisometropia primarily disturbs binocularity thereby causing reduced stereoacuity. Development of stereoacuity is interrelated to similarity in the refractive status of the fellow eyes; fine motor skills which require swiftness and precision of movements are defective in amblyopic children. Therefore, management of anisometropic amblyopia is more prolonged and complex, especially if it is accompanied with strabismus [74]. In distinction to strabismic and deprivational amblyopia, anisometropic amblyopia is more frequently asymptomatic and detected at an older age; only 15% of affected children are diagnosed before they are 5 years of age [75].

Studies demonstrate that the most important factors in treatment results are age and depth of amblyopia that are directly related to the degree of anisometropia [76]. Therefore, as the child gets older, management becomes more complex and time consuming particularly in hypermetropic anisometropes in whom a less encouraging treatment results are seen, in contrast to myopes. It is suggested that in anisometropic subjects, amblyopia is less severe in children younger than 3 years of age and improvement in visual and stereoacuity is more probable if treatment is initiated prior to this age [77, 78]. Based on repeated finding of anisometropia in CNLDO particularly in unilateral anisometropia it is vital to check refractive status of children with CNLDO to assess visually significant anisometropia at an early age to prevent these children from amblyopia and visual morbidity.

## 4.2 CNLDO, anisometropia, and amblyogenic potential

First Chalmers and later Ellis questioned the relationship between CNLDO and visual maturation. Chalmers found anisometropia in 3.8%, in eyes with CNLDO; all

their subjects were hypermetropic in the affected eye [79]. Ellis found no appreciable increased incidence of amblyopia (1.6%) in a large series of 2249 patients with NLDO compared with controls. They also found no correlation between refractive error and NLDO, including no significant increase in the incidence of anisometropia [80].

In our study, the prevalence of anisometropia (greater than 1.5 D) in NLDO patients of 13.7% is approximately thrice that of the general population [81]. It is also higher than reported studies on this subject matter [47, 48, 79–81]. Similarly, a study of around 1200 CNLDO patients found twice the rate of anisometropia in the unilateral CNLDO patients (7.6%) compared with bilateral NLDO patients (3.6%) that the rate of anisometropia and amblyopia is greater in NLDO patients. Anisometropia occurred at a greater rate in unilateral NLDO patients compared with bilateral NLDO patients and occurred at a greater rate in this CNLDO cohort than expected in the general pediatric population. Several patients with anisometropia went on to develop clinical amblyopia [47].

Matta et al. reviewed 375 patients with CNLDO and reported that 22% of the children with CNLDO had amblyopia risk factors [48]. Piotrowski and colleagues described a high prevalence (9.8%) of anisometropia with or without amblyopia in an 8-year consecutive case series which included 305 children with CNLDO [49]. Furthermore, Eshraghi and colleagues studied 433 cases with CNLDO that underwent probing. They reported that 5.5% had anisometropia and 9.46% had amblyopia risk factors. They also found more anisometropia in failed probing cases and theorized that structural abnormality may have a part to play in the development of anisometropia [82].

Bagheri et al. evaluated refractive state in children with unilateral CNLDO; they reported that in children aged 4 years and older, the interocular difference between spherical error and spherical equivalent was considerable as compared to children younger than 4 years [83]. Contrary to this, in our study, we found no significant association between the age (in months) of the patients and the interocular difference in sphere, cylinder, and SE of affected and non-affected eyes. However, when we observed the refractive status of children with CNLDO, we found that as the children age increased the prevalence and severity of refractive error and anisometropia increased. We also observed that difference between the affected and fellow eyes was significant in terms of spherical refractive error and spherical equivalent and that hypermetropia was more common in the eye with CNLDO. These findings illustrate that when unilateral CNLDO becomes chronic, the likelihood and severity of hypermetropia increases which as detailed, is a risk factor for amblyopia [81, 84]. This finding is clinically significant, as management and prognosis of amblyopia becomes intricate in older children.

The published literature proposes that the prevalence of anisometropia increases as the nature of the CNLDO becomes more chronic. Our study on bilateral CNLDO shows that the interocular difference in the mean spherical equivalent of children with unilateral CNLDO increases with the age of the patients. This was not the case in the patients with bilateral CNLDO. Therefore, children with chronic obstruction are more prone to be amblyogenic [85]. Hence, timely resolution of the problem is recommended to avoid visual morbidity, i.e., anisometropia and amblyogenicity.

If the anticipated association between CNLDO and anisometropia is refractory and the persistent epiphora, discharge, and topical medication in the conjunctival cul-de-sac is being held responsible in hampering the physiological emmetropization, then early resolution of CNLDO should retard the development of anisometropia and thus save the child from developing anisometropic amblyopia. However, a study found results contrary to this. Recently, Pyi Son studied 244 cases and found that early and spontaneous resolution of CNLDO is more likely

to have a higher (not lower) rate of anisometropia compared to spontaneous or surgical resolution [86]. They proposed that the eye with CNLDO proceeds to emmetropization differently than the unaffected eye. Early resolution can hinder the process of emmetropization in the affected eye, making it lag behind the normal eye in achieving emmetropization. These findings negate the fact that anisometropia in CNLDO is transient and refractory. Further studies need to be done to determine the timing of resolution of CNLDO and its effect on the development, progression, and resolution of anisometropia and if present amblyopia. In most studies, including the one we conducted, they did not determine whether anisometropia persisted or not after surgical intervention or in later life. Simon reported that even after CNLDO has improved, anisometropic hypermetropia is a regular finding in patients with a history of unilateral CNLDO [87]. Nevertheless, results of all these studies consistently report high rates of anisometropia which concomitantly has amblyogenic effect.

Even though studies suggest that correction of the refractive error in anisometropia alone results in enhances quality of vision in anisometropic amblyopia, it is usually contemplated that most of cases will need added treatment because refractive error adjustment alone will not be adequate to completely manage the depth of amblyopia. Therefore, patching or pharmacological treatment is often prescribed at the same time or soon after the refractive spectacle correction is given. Concrete evidence, generally from the Pediatric Eye Disease Investigator Group, has established both number of hours per day of patching (according to age) and days per week of atropine use as good penalization technique to improve vision and stereoacuity in amblyopia [88]. The use of glasses alone has also been recognized as an excellent first-line treatment for both anisometropic and strabismic amblyopia. IPad-based dichoptic training has shown promising data for vision rehabilitation in amblyopes. Use of pharmaceutical augmentation of traditional therapies has also been investigated. Several different drugs with unique mechanisms of action are thought to improve the receptiveness to amblyopia therapy. However, no data on new treatment options from evidence-based research has surfaced which proves as being better to conventional therapies in regular clinical practice. Continued research into the use of new technology and comprehending the neuronal basis of amblyopia promises alternate or perhaps improved cures in the near future [89].

Studies mention that emmetropia is achievable in anisometropes with appropriate management [90]. However, the precise cause why studies find high prevalence of anisometropia in subjects even after CNLDO has resolved is still contentious. Nevertheless, the results endorse the fact that patients of CNLDO should be regularly reviewed for refractory status. Furthermore, as shown in our results, in older subjects, the interocular difference becomes more significant compared to younger children; this places them at high risk for developing amblyopia. They are also inclined to poor prognosis in terms of visual recovery. These facts support the benefit of early intervention in CNLDO. However, further studies with larger sample size longer follow-up time is required to establish this effect.

## 5. Conclusion

CNLDO should be observed and treated conservatively till the child is 1 year old. If CNLDO does not respond to conservative treatment, then they should be promptly treated with probing and syringing. In cases remission two cycles of syringing and probing, intubation is a reasonable treatment option. Surgical procedures should be reserved for complicated cases. Unilateral CNLDO is a

risk factor for anisometropia particularly hypermetropic anisometropia with amblyogenic potential. Keeping in view that CNLDO is a common presentation in pediatric ophthalmology clinics, we recommend that all children with CNLDO should be regularly followed, even after the obstruction has anatomically and functionally resolved. These children should undergo cycloplegic refraction on each visit and should be monitored for the development of amblyopia and other ocular abnormalities.

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