CASE REPORT

UNVEILING OPHTHALMOLOGICAL FINDINGS IN CORNELIA DE LANGE SYNDROME: A RARE CASE REPORT

Dian Estu Yulia[1], Sabrina Tan[2]
[1]Department of Ophthalmology, Faculty of Medicine Universitas Indonesia, Cipto Mangunkusumo National Central General Hospital, Jakarta, Indonesia
[2]Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
Email: dianestu.dianestu@gmail.com

ABSTRACT

Introduction: *Cornelia de Lange syndrome (CdLS) is a rare congenital disorder with a distinctive combination of physical, cognitive, and behavioral features. This syndrome impacts multiple systems in the body, including the eyes.*

Case Report: *A three-year-old boy with classic CdLS, emphasizing the ophthalmological findings of left eye ptosis, high myopia and astigmatism, microcornea, bilateral "dot opacities" cataracts, and tigroid fundus appearance. The patient was prescribed corrective eyeglasses to prevent amblyopia.*

Discussion: *The clinical scoring system devised by the International CdLS Consensus Group aids in classifying CdLS cases into classic and non-classic variants, as well as guiding clinical genetic testing decisions. In all instances of suspected or confirmed CdLS, it is imperative that an ophthalmologist performs an initial eye examination promptly. Therefore, acquiring familiarity with the potential ophthalmological findings of CdLS is crucial. Common ocular presentations encompass features such as synophrys, thick eyebrows, long eyelashes, ptosis, myopia, microcornea, nasolacrimal duct obstruction, peripapillary pigment ring, and blepharitis. Meanwhile, less frequently encountered ocular manifestations include hyperopia and astigmatism, cataracts, microphalmia, glaucoma, optic nerve pallor and hypoplasia, nystagmus, and strabismus.*

Conclusion: *Timely diagnosis, precise interventions, and regular ophthalmological monitoring are pivotal in preventing complications and enhancing visual function, thus improving the quality of life of individuals with CdLS.*

Keywords: *Cornelia de Lange syndrome, ptosis, high myopia, cataract*

INTRODUCTION

Cornelia de Lange syndrome (CdLS) is a rare congenital disorder that affects multiple systems and manifests with a distinctive combination of physical, cognitive, and behavioral features.[1] Named after Cornelia de Lange, a Dutch pediatrician who first described the disease in two children in 1933, CdLS is estimated to affect between 1 in 10,000 to 1 in 30,000 live births.[2] It impacts both genders equally, with no racial predilection. This syndrome is associated with gene mutations in NIPBL, SMC1A, SMC3, HDAC8, RAD21, and ANKRD11, with most cases resulting from mosaicism and, more rarely, following an autosomal dominant hereditary pattern.

Patients with CdLS present with dysmorphic facial features, hirsutism, developmental delays, growth retardation, limb abnormalities, intellectual disability, behavioral problems, and a range of gastroenterological, cardiac, genitourinary, neurological, otolaryngological, and ophthalmological abnormalities and dysfunctions.[1,6] The manifestations of this disorder can range from mild to severe, with different degrees of organ involvement.[1] Thus, within a multidisciplinary team providing care for individuals with CdLS, ophthalmologists must be well-versed in the ophthalmological aspects of the syndrome. These encompass a range of features, including synophrys, thick eyebrows and long eyelashes, ptosis, blepharitis, nasolacrimal duct obstruction, microcornea, cataract, glaucoma, optic nerve abnormalities, refractive errors, strabismus, and nystagmus.[1,3,7]

This paper aims to report on the multiple ophthalmologic findings in a three-year-old boy with CdLS and emphasize the crucial role of ophthalmologists in optimizing visual development.

CASE ILUSTRATION

A 3-year-old boy was referred to the Pediatric Ophthalmology Division from the Pediatric Department of the Cipto Mangunkusumo National Central General Hospital, Jakarta, Indonesia, for a comprehensive ophthalmological evaluation. The referral was made due to suspicions of CdLS.

The boy is the older of two siblings. She received regular prenatal care and had no history of miscarriages. There is no family history of consanguinity or hereditary diseases. The child was delivered at full term through natural childbirth, with a birth weight of 2,350 g and a birth length of 43 cm. There was no history of respiratory failure, sepsis, or treatment in the neonatal intensive care unit (NICU) following delivery. The mother and child were discharged from the hospital simultaneously.

The mother reported that the child has had a drooping upper left eyelid since birth. Furthermore, since infancy, the child frequently vomited during and after meals and after coughing, which subsided when given anti-emetic medication, strongly suggesting gastroesophageal reflux. There was a history of one seizure at age two years and six months. The child exhibited speech delay with the ability to babble only at three years old, relied on gestures for communication, and inconsistently responded when called.

The physical examination revealed several distinctive features, including thick eyebrows with synophrys, long eyelashes, unilateral ptosis, a short nose with an upturned nasal

tip, smooth philtrum, downturned corners of the mouth, micrognathia, hirsutism, low set ears, a short neck, low posterior hairline, syndactyly, and bilateral undescended testis. Some of these features are depicted in Figure 1. Anthropometric assessment indicated growth retardation (< -3 SD) and microcephaly (< -3 SD). An otolaryngologist conducted audiological tests and identified profound sensorineural hearing loss. A complete blood work, urine analysis, chest X-ray, and echocardiogram showed no abnormalities.

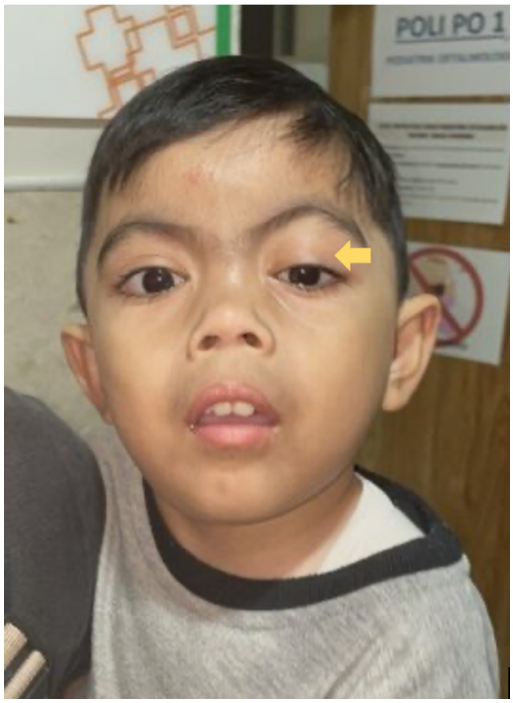

Figure 1. Classic craniofacial features of CdLS in the patient, including unilateral ptosis.

During the initial visit to the pediatric ophthalmology department, the child presented with ptosis in the left eyelid, measuring a marginal reflex distance (MRD) of +1 and with no lid crease. The fundus examination showed normal findings. Subsequent examination with streak retinoscopy led to the diagnosis of high myopia with compound myopic astigmatism in both eyes and congenital ptosis of the left eye.

One month later, the child underwent an examination with an automated refractor and retinal camera under general anesthesia. Interpupillary and intercanthal distances were 50 mm and 25 mm, respectively. The axial length of the right eye was 20.98 mm, while the left eye measured 21.55 mm. The autorefractor measurements for the right eye revealed -4.75 D (S), -4.75 D (C), and 179° (A), whereas the left eye showed -5.00 D (S), -4.75 (C), and 1°(A). These findings confirmed the diagnosis of bilateral high myopia with compound myopic astigmatism.

The intraocular pressure measurements were within the normal range for both eyes, which were 13.8 mmHg in the right eye and 15.5 mmHg in the left eye.

During the examination of the anterior segment of both eyes, the conjunctiva exhibited a pale appearance, with no signs of blue sclera. The cornea was clear with a diameter of 10 mm, the anterior chamber angle was wide open, pupils were dilated due to mydriatics, and cataract morphology presented as “dot opacity” located centrally on both eyes (Figure 2). The optic discs in both eyes appeared round and pale pink, with a defined cup-to-disc ratio measuring between 0.3 and 0.4. A positive macular reflex was observed. Additionally, both eyes displayed tigroid fundi (Figure 3). The child was prescribed eyeglasses and scheduled for regular monitoring.

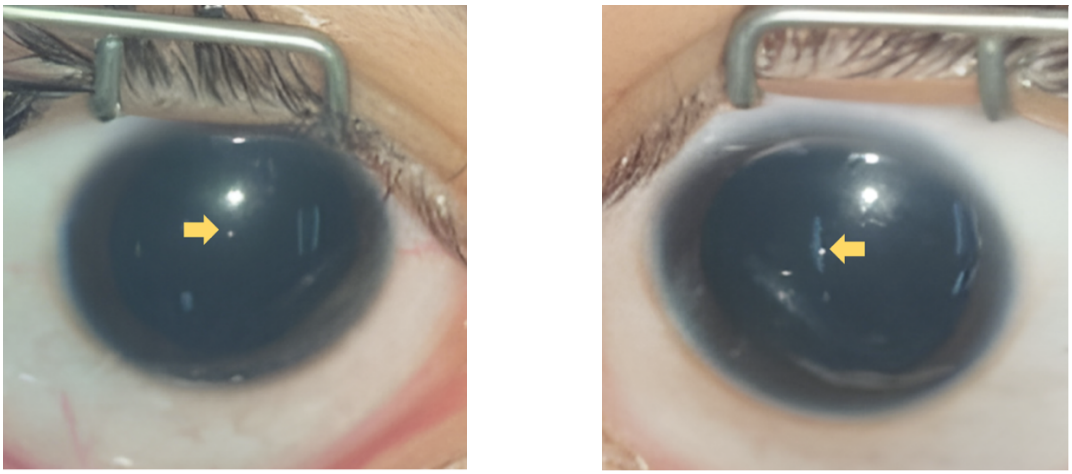

Figure 2. An anterior segment examination shows microcornea and "dot opacities" cataracts (yellow arrow) in both the right and left eyes.

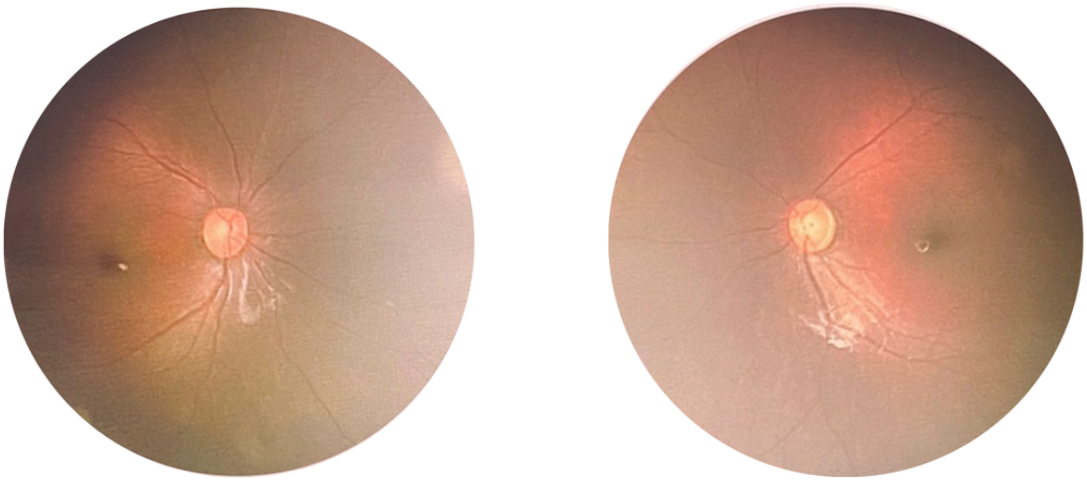

Figure 3. Bilateral posterior segment examination showing tigroid fundus appearance.

DISCUSSION

Cornelia de Lange Syndrome (CdLS) is a congenital syndrome characterized by a broad range of features that vary in severity from mild to severe.[1,6] To address the variability in CdLS presentations, the International CdLS Consensus Group introduced a clinical scoring system in 2018. This system is based on cardinal and suggestive features (Table 1) and aids in making decisions regarding clinical genetic testing.[1]

Table 1. Clinical Scoring System of CdLS by the International CdLS Consensus Group[1]

Cardinal Features (2 points each if present)
• Synophrys and/or thick eyebrows
• Short nose, concave nasal ridge and/or upturned nasal tip
• Long and/or smooth philtrum
• Thin upper lip vermilion and/or downturned corners of mouth
• Hand oligodactyly and/or adactyly
• Congenital diaphragmatic hernia
Suggestive Features (1 point each is present)
• Global developmental delay and/or intellectual disability
• Prenatal growth retardation
• Postnatal growth retardation
• Microcephaly (prenatally and/or postnatally)
• Small hands and/or feet
• Short fifth finger
• Hirsutism
Clinical Score
• 11 points, of which at least 3 are cardinal features: classic CdLS
• 9-10 points, of which at least 2 are cardinal features: non-classic CdLS
• 4-8 points, of which at least 1 is a cardinal feature: molecular testing for CdLS indicated
• <4 points: insufficient to indicate molecular testing for CdLS

According to this scoring system, the patient in this report has a clinical score of 12. This score is derived from the presence of four cardinal features (synophrys and thick eyebrows; short nose and upturned nasal tip; long philtrum; and downturned corners of the mouth) and four suggestive features (global developmental delay; postnatal growth retardation; postnatal microcephaly; and hirsutism). These findings collectively indicate a classic presentation of CdLS. The patient also exhibits other signs and symptoms associated with CdLS, including GERD, bilateral cryptorchidism, seizure, and profound sensorineural hearing loss.

Up to 80% of all CdLS patients have ophthalmologic abnormalities or dysfunction.[1] Synophrys, thick eyebrows, and long eyelashes are the predominant periocular characteristics in individuals with CdLS.[7] Although both unilateral and bilateral ptosis can be present in CdLS, bilateral ptosis is more commonly found (44%) than unilateral ptosis (37%).[1] Studies have

found a higher incidence of ptosis in patients with NIPBL mutations, suggesting a potential association with the pathogenesis of ptosis.[3] Notably, over half of the patients with ptosis (57%) present with compensatory chin lift, which interferes with their ambulation. Surgical intervention may be considered in cases where compensatory chin lift significantly impacts ambulation amblyopia or refraction errors due to ptosis.[7] In this report, the patient presents with unilateral ptosis; however, there is currently no indication for ptosis correction surgery.

Refractive error is a common ophthalmological manifestation of CdLS, with myopia being the most prevalent. A study by Levin et al. reported a myopia prevalence of 60% in their research cohort.[8] A more recent study by Wygnanski-Jaffe et al. found a myopia prevalence of 58% in their cohort, with 38% of these individuals having a spherical equivalent of >5.0 D and 9% having a spherical equivalent of >10.0 D. Hyperopia and astigmatism are less common in CdLS.[7]

The patient in this report underwent an examination under anesthesia, which revealed bilateral high myopia and astigmatism with a spherical equivalent of -9.8 D. Consequently, the patient was prescribed eyeglasses. Studies have shown refusal in children with CdLS to wear glasses. However, correcting refractive errors is crucial and should be initiated as early as possible to prevent amblyopia.[1]

Cataracts, along with microphthalmia and glaucoma, are uncommon anterior segment anomalies in CdLS. Both unilateral and bilateral cataracts are rare in CdLS. It is important to note that in patients with CdLS, cataracts may result from self-inflicted injuries, particularly when accompanied by other signs of trauma, such as corneal ulcers, hyphema, vitreous hemorrhage, and retinal detachment. [3] The patient in this report had bilateral “dot opacities” cataracts, and given the absence of other signs of trauma, CdLS is the likely underlying cause of cataracts. Additionally, the patient presented with tigroid fundus, which is a finding also documented in a case report from Korea.[9]

Microcornea is defined as a corneal diameter of 10 mm or smaller in children older than two years or 9 mm or smaller at birth.[10] According to these criteria, the patient’s corneal size in this report meets the definition of microcornea. A study by Wygnanski-Jaffe et al. found that microcornea was found in 21% of children in their cohort.[7] Other common ocular findings typically associated with CdLS, such as nasolacrimal duct obstruction, peripapillary pigment ring, and blepharitis, were not evident in the patient. Less commonly encountered ocular findings, such as optic nerve pallor, optic nerve hypoplasia, nystagmus, and strabismus, were also absent in this patient.[3]

The various manifestations of CdLS necessitate a holistic and multidisciplinary approach to ensure optimal patient care.[1] Patients with CdLS may have ocular manifestations; thus, ophthalmologists should familiarize themselves with the possible presentations and their impact on vision. In all cases of suspected or confirmed CdLS, conducting an initial eye examination as early as possible is imperative to enable prompt treatment. Furthermore, regular follow-up appointments should be scheduled to monitor changes in ocular health and adjust treatment as needed. These measures aim to prevent irreversible ocular complications such as vision loss due to amblyopia and improve overall visual function.[3]

CONCLUSION

Cornelia de Lange Syndrome (CdLS) is a rare congenital disorder with manifestations that span a spectrum from mild to severe. In this care report, the child presents with classical CdLS features, with ophthalmological abnormalities and dysfunction such as synophrys, thick eyebrows, long eyelashes, unilateral ptosis, bilateral high myopia, and astigmatism, bilateral "dot opacities" cataracts, and tigroid fundus appearance. This case highlights the complexities of CdLS and the importance of a multidisciplinary approach, particularly emphasizing the crucial role of ophthalmologists. Through the early implementation of ophthalmologic examinations, accurate interventions, and consistent follow-up, ophthalmologists strive to prevent ocular complications and enhance visual function. This comprehensive approach offers hope for improving the overall quality of life for individuals with CdLS.

REFERENCES

1. Kline AD, Moss JF, Selicorni A, Bisgaard AM, Deardorff MA, Gillett PM, et al. Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement. Nat Rev Genet. 2018; 19:649–66.
2. Kline AD, Grados M, Sponseller P, Levy HP, Blagowidow N, Schoedel C, et al. Natural history of aging in Cornelia de Lange syndrome. Am J Med Genet C Semin Med Genet. 2007;145C:248–60.
3. Shi A, Levin AV. Ophthalmologic findings in the Cornelia de Lange syndrome. Ophthalmic Genet. 2019; 40:1–6.
4. Huisman SA, Redeker EJW, Maas SM, Mannens MM, Hennekam RCM. High rate of mosaicism in individuals with Cornelia de Lange syndrome. J Med Genet. 2013; 50:339–44.
5. Nallasamy S, Kherani F, Yaeger D, McCallum J, Kaur M, Devoto M, et al. Ophthalmologic findings in Cornelia de Lange Syndrome: a genotype-phenotype correlation study. Arch Ophthal. 2006; 124:552–7.
6. Boyle MI, Jespersgaard C, Brøndum-Nielsen K, Bisgaard AM, Tümer Z. Cornelia de Lange syndrome. Clin Genet. 2015; 88:1–12.
7. Wygnanski-Jaffe T, Shin J, Perruzza E, Abdolell M, Jackson LG, Levin AV. Ophthalmologic findings in the Cornelia de Lange syndrome. J AAPOS. 2005; 9:407–15.
8. Levin A V., Seidman DJ, Nelson LB, Jackson LG. Ophthalmologic findings in the Cornelia de Lange syndrome. J Pediatr Ophthalmol Strabismus. 1990; 27:94–102.
9. Kim IT, Park JW, Choi WC. A Korean case of Cornelia de Lange syndrome. Korean J Ophthalmol. 2005; 19:153–5.

10. American Academy of Ophthalmology. Pediatric Ophthalmology and Strabismus. In: Khan A, Chang TCP, El-Dairi MA, Lee KA, Utz VM, Mireskandari K, et al., editors. 2022-2023 Basic and Clinical Science Course. American Academy of Ophthalmology; 2022.