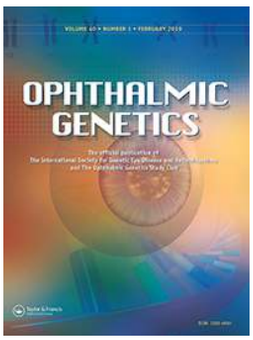

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REVIEW

Ophthalmologic findings in the Cornelia de Lange syndrome

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ABSTRACT

Background: Cornelia de Lange syndrome (CdLS) is a congenital disorder characterized by multisystem abnormalities, including distinct ophthalmologic findings. In recent years, advances in molecular genetics have begun to provide new insight into the characterization of these clinical features and the genetic basis of the syndrome. Materials and methods: We included 37 articles that were identified through an electronic search in PubMed and through the reference lists of previously conducted reviews. Studies of 30 or more patients were used to report frequencies of common and less common findings. Genotype–phenotype studies were used to provide additional information when available. Results: Ocular anomalies are present in most patients with CdLS. Common findings include long eyelashes, synophrys, hirsutism of the eyebrows, peripapillary pigment ring, and myopia. Less common findings include hyperopia, ptosis, blepharitis, short palpebral fissure length, down-slanting palpebral fissures, mild microcornea, strabismus, nystagmus, and optic nerve abnormalities. Conclusions: This review provides a comprehensive summary of the ophthalmologic findings in CdLS. Mutations in certain genes may be associated with specific ocular abnormalities, although future genotype studies are needed to further characterize these relationships.

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KEYWORDS
Cornelia de Lange syndrome; eye abnormalities; genetics

Introduction

Cornelia de Lange syndrome (CdLS) is a congenital disorder characterized by multisystem abnormalities, including characteristic craniofacial features (Figure 1), hearing loss, distal limb anomalies (Figure 2), growth and developmental delays, gastroesophageal reflux disease, and other features (1,2). The syndrome has been found to be associated with mutations in *NIPBL, SMC1A, HDAC8, SMC3*, or *RAD21* (3). A clinical review of 181 affected individuals demonstrated that ocular anomalies were present in 57% (4). Common ocular findings reported in the literature include long eyelashes, synophrys, hirsutism of the eyebrows, peripapillary pigment ring, and myopia. Less common findings, seen in >5% of patients, include hyperopia, ptosis, blepharitis, short palpebral fissure length, down-slanting palpebral fissures, mild microcornea, strabismus, nystagmus, and optic nerve abnormalities. In this review, we summarize the incidence, impact on visual function, management, and genetic correlates (when available) for ophthalmologic findings in CdLS.

Methods

Articles were identified through an electronic search in PubMed and through the reference lists of previously conducted reviews. Those that only described ocular findings already presented in larger studies were excluded. The 37 remaining articles contained 680 cases, which were comprised of reports of specific ocular anomalies in a single patient, reports of general ocular findings and manifestations of CdLS, and small case series that included descriptions of ophthalmologic abnormalities as part of a systemic evaluation. There were 9 studies that included 10 or more patients and 4 studies that included more than 30 patients. One of these studies, which included 310 patients, noted the prevalence of characteristic findings (long eyelashes, synophrys, hirsutism of the eyebrows) and of "ocular anomalies" but did not describe them in further detail. Studies of >30 patients were used to report frequencies of common (present in >50% of patients) and less common findings. Uncommon findings were considered to be those present in <5% of patients or, for findings that had no reported prevalence, reported in 3–10 patients. We also reviewed case reports to identify unique or rare findings defined as those occurring in only 1–2 patients, acknowledging that in some cases, these findings may have occurred by chance. Most case reports did not provide additional discussion or explanation of possible associations for these rare findings, but when applicable these comments are provided in their respective sections. The majority of studies examined patients based on a clinical diagnosis of CdLS, but those which provided genotype information are specifically noted. Of the cases included, 79 patients had a positive genotype, including one patient with a *SMC1A* mutation, 43 patients with *NIPBL* mutations, and 35 patients with *HDAC8* mutations who all had "clinical features that overlap those seen in CdLS," although few of these latter patients had features that were fully consistent with the classical phenotype (5–10). We did not include studies that included genotype information but that did not include detailed ophthalmologic findings. To our knowledge, with the exception of one study based on ophthalmologic records and survey responses from

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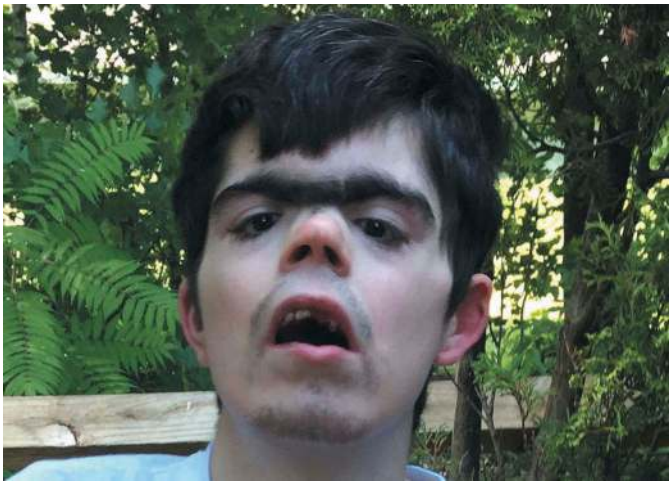

Figure 1. Classic craniofacial features of CdLS: synophrys*, thick eyebrows*, long eyelashes; short nose*, upturned nasal tip*; long, smooth philtrum*; low-set ears.

*Considered to be cardinal diagnostic features.

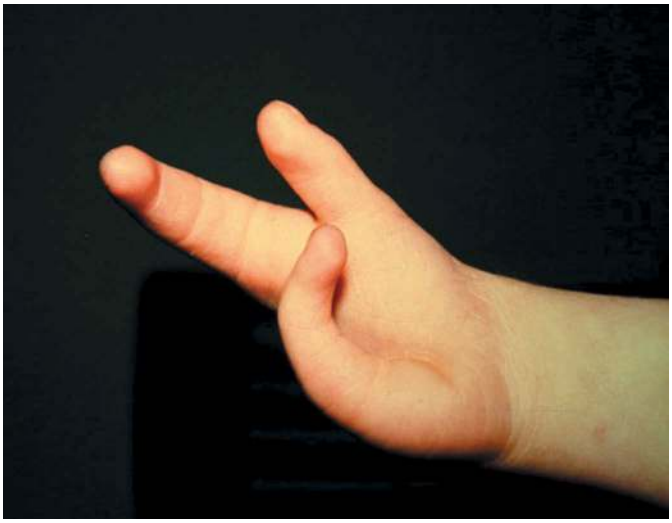

Figure 2. Characteristic limb reduction deficit seen in CdLS.

parents (5), all studies included in this review involved ophthalmic examination of the subjects, although a complete ocular examination is often difficult to obtain in patients with CdLS (11). Consequently, frequency rates for many ocular findings may be higher or lower than reported in the literature, particularly for abnormalities of the posterior segment. Certain assessments, such as refractive error, corneal diameter, and assessment for hypertelorism or telecanthus, were obtained by gross examination when direct measurement was not possible.

Results

Refractive error

Myopia is observed in 57–58% of children with CdLS and can range from mild (−0.5 to <−3.0 D) to high (≥−5.0 D) (5,11–18). One large study reported that 38% of patients had a spherical equivalent of >5.0 D, and 9% had a spherical equivalent of >10.0 D (11). Other reports have noted severe myopia as high as −28.0 D (17). A study of individuals with *HDAC8* mutations noted myopia in 11/25 (44%) (6). A genotype–phenotype correlation study showed no significant correlation between *NIPBL* mutations and the presence of myopia, nor any difference in myopia severity between mutation-positive and mutation-negative groups (5). This study also showed that hyperopia is less common, with a prevalence up to 15% (8/54); 5 of these 8 hyperopic patients were *NIPBL* mutation-positive. Comparison was not made to age-adjusted normative values. This low percentage may reflect the normal hyperopia of childhood at a decreased incidence due to the high incidence of myopia. Astigmatism has also been noted (17), including one case of CdLS due to *SMC1A* mutation (8) and cases of both *NIPBL* mutation-positive and negative CdLS (5).

Refraction should be performed as early as possible to prevent amblyopia, although children may refuse glasses and occlusion therapy may be difficult. In a study of 22 children with CdLS, 3 had been prescribed glasses but refused to wear them (13) and in a group of 120 children who underwent ophthalmic examination, none were wearing glasses at the time of the exam (11). Contact lenses are effective for high myopia and may provide better vision-related quality of life than spectacles in children (19), but the behavioral challenges and aversion to face touching in patients with CdLS usually make this impractical. We are aware of very few patients with CdLS who have been successful in contact lenses. Surgical refractive procedures may improve visual function when children have difficulties with both glasses and/or contact lenses (20). Refractive surgery (including photorefractive keratectomy, phakic intraocular lens implantation, and clear lens extraction/refractive lens exchange) has been performed on special needs children with high myopia with good visual improvement (21). Intraocular collamer lens implantation in spectacle-aversive special needs children has also been shown to significantly improve vision, although results may be limited by visual or ocular comorbidities (22). To our knowledge, these techniques have not yet been applied to children with CdLS.

Periocular findings

The largest study in which the intercanthal distance was measured in patients indicated that telecanthus (60%) is more commonly found than hypertelorism (30%) (11). A study of 34 patients with *HDAC8* mutations and CdLS-like features described hypertelorism in 47% and telecanthus in 64% (6). Nicholson et al. reviewed 48 cases and also noted telecanthus, but not hypertelorism (23). In a report of 12 cases of CdLS that were based on clinical diagnosis, 16.6% demonstrated hypertelorism (24) although no description of methodology was reported. The methodology of measurement does greatly influence the interpretation of the oculofacial findings (13).

The most commonly described ocular findings in CdLS include long eyelashes (present in 99% of patients), synophrys (98–99%), and hirsutism of the eyebrows (78–96%), as noted in large studies of 310 patients (4) and 120 patients (11). They have been shown to be present in genotype-confirmed cases of CdLS involving mutations in the *NIPBL*, *SMC1A*, and *HDAC8* genes (6–10), although prevalence may vary with

the mutated gene. In individuals with *HDAC8* mutations, long eyelashes were found in 14/31 (45%), synophrys in 30/33 (90%), and hirsutism in 21/32 (65%) (6). These characteristic findings may be present even when patients demonstrate no other obvious ocular abnormalities (23,25).

Rare findings which have been reported in only 1–2 cases include "deep-set eyes"/enophthalmos (15,24,26–28), exophthalmos/proptosis (5,29), phthisis (5), and paresis of the orbicularis oculi muscle (12,30), with "nonelevated capillary hemangiomas" over both upper lids in one patient (12).

Eyelids

Ptosis has been reported in 44% of clinically diagnosed patients by ophthalmic examination, and may be bilateral (63%) or unilateral (37%) (11). In a study of 28 patients who were tested for mutations in the *NIPBL* gene, "ptosis and ocular abnormalities" were found in 7/13 (54%) of mutation-positive patients and 8/15 (53%) of mutation-negative patients (10). Park and coworkers also noted bilateral ptosis in a case of CdLS caused by a missense mutation in the *NIPBL* gene (7). Another study of 54 previously genotyped CdLS patients showed slightly higher rates of ptosis (58%, laterality not specified) among patients with *NIPBL* mutations compared to *NIPBL* mutation-negative patients (36%), although this result was not statistically significant (5). There was no difference in ptosis severity between the two groups, although within the mutation-positive group there was a slight, nonsignificant trend toward increased ptosis severity in individuals with truncating mutations compared to individuals with missense mutations ($p = 0.07$), suggesting that *NIPBL* mutations may be associated with ptosis pathogenesis. In a study of 32 patients with *HDAC8* mutations, 18% demonstrated ptosis (laterality not specified) (6). In the same study, hooding of the eyelids or "redundant overfolded skin of the upper eyelids" was described in 46%. This has not been observed in other studies and may be suggestive of, or specific to, a CdLS phenotype caused by *HDAC8* mutations. Ptosis is usually associated with poor levator palpebrae function (13,31). Surgery may be indicated for visually significant ptosis, particularly when patients demonstrate a compensatory chin lift, which may be present in up to 57%, or when amblyopia or refractive error is thought to be secondary to the ptosis (11). Some children have such prominent chin lifts that it interferes with ambulation and the ability to look up.

Blepharitis is noted in 25% of patients (11). Many patients may also report a history of blepharitis-related symptoms, including epiphora, "conjunctivitis," ocular discharge, chalazions/styes, and recurrent red eyes or red lid margins which may occur with or without evidence of blepharitis upon examination (5,11,12,15). These symptoms can be particularly uncomfortable and bothersome for young children and may be confused with nasolacrimal duct obstruction. Treatment of blepharitis in the form of lid hygiene (baby shampoo or proprietary scrubs) is very effective. Probing or more invasive treatments for nasolacrimal duct obstruction should be considered only when symptoms are not improved with presumptive treatment for blepharitis (11).

Horizontally short palpebral fissures were measured indirectly (through calculations from measured outer and inner canthal distances) in 31% of examined patients (11). Down-slanting palpebral fissures are described in 7% of patients (11) and may be unilateral, as described in one case (13), while up-slanting is even less common (16,32). Epicanthal folds are uncommon, but have been reported (13,16,24). Rare eyelid findings include entropion in two patients, one of whom required entropion correction surgery (5,14) and bilateral distichiasis in one patient (33).

Nasolacrimal findings

Nasolacrimal duct obstruction, unilateral or bilateral, has been found in 67–80% of patients (5,11,34). A study of individuals with *HDAC8* mutations found nasolacrimal duct obstruction in 6/25 (24%) (6). In a genotype–phenotype correlation study of 54 patients, there was no significant correlation with nasolacrimal duct obstruction, nor any significant difference in severity of nasolacrimal duct obstruction, between *NIPBL* mutation-positive and *NIPBL* mutation-negative groups (5). Additionally, there have been reports of bilaterally absent upper lacrimal puncta and canaliculi with small lacrimal sacs (35), as well as unilateral and bilateral nasolacrimal fistulae (13,14). Surgical probing and irrigation may be indicated for nasolacrimal duct obstruction if blepharitis treatment fails. Severe nasolacrimal duct obstruction may require nasolacrimal intubation and/or dacryocystorhinostomy.

Anterior segment

Anterior segment abnormalities include microcornea, and less commonly, microphthalmia, cataract, and glaucoma. The only large-scale study that included assessment of microcornea in patients found a prevalence of 21% (11). Microphthalmia is uncommon but has been reported in a few cases (12,16,33), including three patients with *NIPBL* mutations (missense, nonsense, and frameshift) (5). Unilateral or bilateral cataracts are uncommon and found in both *NIPBL* mutation-positive and mutation-negative individuals (5). Reported cataract morphologies include Mittendorf dot, "dot opacities," posterior subcapsular, Morgagnian, and anterior cortical (5,11,33,35). One report also described a patient who had a complete cataract with a "greenish hale" in both eyes that had developed over 3 years (15). Other authors evaluated this case in retrospect wondering if this could have represented Coats disease (see below) (31). Cataract may also be the result of self-injurious behavior documented in this case and in many other affected patients, along with other ocular issues or signs of trauma including corneal ulcers, hyphema, hypotony, iris atrophy, iris neovascularization, recession of the anterior chamber angle, posterior synechiae, vitreous hemorrhage, and retinal detachment (11,13,15).

Rare findings of the anterior segment include corectopia (12,16), partial pupillary membrane (12), and iris thinning (33). In one case, there was anisocoria and an irregularity of the pupillary annulus minor, which was absent superiorly in both eyes (23). One case has been reported with bilateral aniridia, posterior embryotoxon, and congenital glaucoma (36). As aniridia and congenital glaucoma are themselves rare diagnoses, the authors question whether there may be an association with CdLS, although this is difficult to assess given the limited number of prior studies with complete and detailed ophthalmic examinations in patients

with CdLS. To our knowledge, four cases of congenital glaucoma have been reported (5,9,36) and in three of these cases, the patient had a frameshift mutation in the *NIPBL* gene (no genotype analysis was performed for the remaining patient). One of these patients also had mosaic Turner syndrome (9). Another child was reported with "secondary aniridia," glaucoma, and retinoblastoma in one eye (described below) (37). One case of Peters anomaly has been reported in an infant who underwent corneal transplantation and later developed glaucoma (38). Other patients with corneal scars and opacities have been reported, but these may have been due to chronic blepharoconjunctivitis (12,15). Although some older reports have documented the finding of blue sclerae (12,24,37,39), this has not been noted in any recent series.

Posterior segment

Wygnanski-Jaffe and coworkers reported that 96% of patients had a normal retina examination although this percentage was from a total of 48 patients who were able to tolerate a retinal examination, and 11% had normal optic discs (11). Fundus examinations in children with CdLS are often limited by behavioral factors, and the prevalence of retinal and optic disc findings may be underrepresented in the literature as a result. Optic nerve abnormalities have been reported in individuals with and without mutations in the *NIPBL* gene (5). A peripapillary pigment ring is common and may be found in up to 83% (11). Other posterior segment findings are uncommon or rare. Optic nerve pallor has been reported in 10 cases (5,11,13,14,26,30,39), and concurrent findings, each present in one patient, included temporal dragging of the macular vessels in both eyes (11), narrowed arteries (39), "temporal hemorrhage" (translated from German) (26), and pallor of the retina (12). One case of optic nerve hypoplasia has been reported in a patient with a nonsense *NIPBL* mutation, and another case of borderline optic nerve hypoplasia with foveal hypoplasia occurred in a *NIPBL* mutation-negative patient (5). Rarely, the optic discs may be cupped and/or tilted bilaterally (5,13). Tilting may be a manifestation of axial myopia.

Four cases of coloboma have been reported, one of which involved the optic disc and at least one of which was bilateral (5,18,26,40). In one case, the coloboma occurred in an *NIPBL* mutation-negative individual (no genotype information was provided for the remaining three patients) (5). Coats disease of various stages has been noted in at least three patients (31,41,42). Three reports of retinal pigmentary changes (5,13) and one report of peripapillary mottling with a "single fleck of pigment nasal to the disc in the midperiphery" (23) have been documented. Poor macular reflexes have been reported in two cases (13). Patients may have retinal detachment or breaks, posterior staphylomas, and tigroid fundus, likely related to axial myopia (5,13,14).

Other unique findings, present in only one known case, include persistent fetal vasculature (43), peripapillary "choroidal crescents," (33) cicatricial chorioretinitis (15), megalopapilla (41), optic disc pit with a relative afferent pupillary defect (40), "a large inferotemporal retinoschisis four disk diameters from the macula" and a choroidal nevus (which occurred in a child who had been born prematurely) (39), vitreoretinal traction/adhesion/fibrosis (5), unilateral retinoblastoma with staphyloma (37) (which was noted to be an incidental finding given the lack of bilateral involvement and negative family history), "extremely large veins" on the optic nerve heads bilaterally (12), and "retinopathy" which was present in a child with a frameshift mutation in the *NIPBL* gene (9).

Nystagmus and ocular alignment

Nystagmus is found in approximately 14–17% of patients with CdLS (5,11), and is most often horizontal pendular (11), although intermittent (13,17), irregular horizontal (28), rotary (15,16), lateral gaze (12), searching (13), latent (40), constant coarse nystagmus (12), or nystagmus in all fields of gaze (16) have been used as descriptors. The genotype–phenotype study by Nallasamy and coworkers found that seven of the nine patients with nystagmus had an *NIPBL* mutation (two missense, two nonsense, and three frameshift); the remaining two patients were *NIPBL* mutation-negative (5). Visual acuity was reported only for one child, who had latent nystagmus and dissociated vertical deviation in the right eye along with a right optic disc coloboma (40). In this case, vision in the right eye was finger counting at 2 m. Levin et al. noted in their study that of eight children with nystagmus, all but one had good, central, maintained fixation (13). Otherwise, visual acuity was either not explicitly documented or not done as few children with CdLS are able to complete a quantitative visual acuity assessment (11).

Strabismus is found in 16–26% of patients (5,11), with esotropia occurring at a higher frequency than exotropia (61% vs. 39%, respectively). In some cases, the esotropia may exceed 60 prism diopters (13). Reports of patients with alternating exotropia (33,44), intermittent exotropia (13), exophoria at near (33), hypertropia (13), or dissociated vertical deviation (40) have appeared. In the study by Nallasamy et al., there was a higher prevalence of strabismus among patients with *NIPBL* mutations (34.6%) than among patients without (21.4%) (5). The mutation-negative patients were more likely to have more severe strabismus ($p = 0.09$); the only two patients who required strabismus surgery were *NIPBL* mutation-negative. Management of strabismus in patients with CdLS is the same as for that of unaffected patients.

Discussion

Advances in genetic techniques over the past decade have contributed to a broader understanding of CdLS, which classically has been diagnosed based on clinical features. Molecular studies have allowed for the identification of specific genes which when mutated result in the classic syndrome (*NIPBL*) or similar phenotypes (*SMC1A, HDAC8, SMC3, RAD21*, and likely others) (2,3). These genes participate in the formation of the multisubunit cohesin protein complex that regulates DNA replication and gene expression (2). Genotype–phenotype correlation studies have been published (5,45), although additional studies are needed to further elucidate these relationships, particularly for ophthalmologic findings.

The expansion of genetic information not only furthers our understanding of pathogenetic mechanisms contributing to CdLS but allows for clinicians to provide improved, informed care. For example, the possible genotype–phenotype correlations

between increased ptosis severity in patients with truncating mutations in *NIPBL* compared to missense mutations, as well as the higher prevalence rates of nystagmus and strabismus in patients with *NIPBL* mutations, may suggest clues to the pathogenesis of these ocular problems, although these differences were not shown to be statistically significant (5). Certain genes have also been implicated in atypical presentations of CdLS, including hyperopia and astigmatism associated with an *SMC1A* mutation (8), hooding of the eyelids associated with *HDAC8* mutations (6), and congenital glaucoma in three patients with *NIPBL* mutations (5,9). While unusual and uncommon, some of these ocular findings may have a significant impact on vision. Although all patients with CdLS should undergo routine eye examinations, those who present with gene mutations known to be associated with specific eye conditions should be more carefully screened for the development of these problems, thereby allowing for earlier treatment and appropriate intervention if warranted. Future studies should continue to clarify these associations.

Individuals with CdLS may have multiple treatable ocular conditions including myopia, ptosis, blepharitis, nasolacrimal duct obstruction, and cataract or retinal detachment secondary to myopia or self-induced ocular trauma. We recommend that patients have an initial ophthalmic examination when a diagnosis of CdLS is first made, in order to establish a baseline and to assess for the presence of abnormalities that would benefit from early intervention. Early intervention may greatly improve function and prevent vision loss due to amblyopia. For nonamblyogenic ptosis, a compensatory chin lift may significantly affect ambulation. Surgical evaluation may occur as early as 12–14 months old, when children begin to walk (46). Blepharitis-related symptoms such as discharge or epiphora are not uncommon, may arise at any age, and may mimic recurrent conjunctivitis or nasolacrimal duct obstruction. Lid hygiene (baby shampoo or proprietary scrubs) is recommended as a presumptive treatment for blepharitis prior to intervention for these other diagnoses unless they are readily apparent. Examination under anesthesia may be required in some patients to adequately assess for any abnormalities, and to obtain a good refraction as well as an inspection of the retinal periphery in children with long axial length. This examination may also be performed in conjunction with other medical procedures requiring general anesthesia.

This review provides an overview of the ophthalmologic findings in CdLS. Initial ophthalmic examination followed by routine annual screening is warranted when a diagnosis of CdLS is made, given that ocular anomalies are present in the majority of patients and may impact vision and daily functioning. Mutations in *NIPBL, SMC1A*, and *HDAC8*, in particular, have been shown to be associated with specific ocular abnormalities, although additional studies are needed to further characterize the genotype–phenotype relationships in this syndrome.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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