Cornelia de Lange Syndrome (CdLS)

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**Patient and History of Present Illness**

A six month-three day old Caucasian infant presented to the eye clinic for a follow-up appointment. His mother stated that he is “off balance a lot” and “gets purple spots around his eyes because he gags a lot”. She also noticed that he has a “keyhole shape in his right eye” and has excessive tearing with “gooey eyes”. The patient was born at thirty-eight weeks with a frank breech and Cesarean section. It was also reported that the patient was not breathing at the time of birth. His past surgical history included multiple gastrointestinal surgeries. His medications included Prevacid and Omnicef, and he had no known allergies to any drugs.

**Patient Examination**

His corrected Teller visual acuity was measured to be 3.2 cycles per centimeter at fifty-five centimeters in both eyes. The normal Teller visual acuity ranges from 2.4 to 13.0 cycles per centimeter. The patient was able to fix and follow
with both eyes, and both pupils were equal, round, reactive to light and
accommodation with no RAPD. Upon external examination, it was noted that he had
mild left upper lid ptosis. He also had long eyelashes, synophrys and excessive
tearing in both eyes. His motility examination revealed a twenty-prism diopter right
intermittent exotropia by a brief Krimsky test. His slit lamp examination was
unremarkable. Dilated fundus examination showed a cup-to-disc ratio of 0.4 in both
eyes. At the conclusion of his exam, he was diagnosed with congenital ptosis of the
left upper eyelid, epiphora in both eyes, and a nasolacrimal duct obstruction of the
right eye, and approximately four diopters of myopia in each eye.

**Introduction:**

Cornelia de Lange Syndrome (CdLS) is a congenital genetic disorder that
affects several parts of the body, its growth, and development. It is named after
Cornelia de Lange, a Dutch pediatrician who, in 1933, described patients that had
similar characteristics that are presently noted as the classic signs of CdLS. Cornelia
de Lange Syndrome is also known as Brachmann-de Lange Syndrome or Amsterdam
Dwarf Syndrome.

**Inheritance**

Cornelia de Lange Syndrome is genetic disorder caused by a mutation in one
of three genes: NIPBL, SMC3, and SMC1A. The proteins derived from these genes
help direct human growth and development before birth. NIPBL, or nipped b-
homolog, produces delangin, which is a substance that aids in human development.
Over fifty percent of cases of CdLS are due to mutations in the NIPBL gene. SMC3
helps to regulate the structure and organization of chromosomes. Mutations in the NIPBL and SMC3 genes are considered autosomal dominant. SMC1A gene is responsible for regulating the structural maintenance of all these proteins. A mutation on the SMC1A gene is considered to be x-linked inheritance.

**Prevalence**

According to the Cornelia de Lange Syndrome Foundation, CdLS occurs in approximately one in ten thousand live births. It equally affects both genders and is seen in all races.

**Ocular Signs of CdLS**

The ophthalmologic findings in patients with Cornelia de Lange Syndrome aid in its clinical diagnosis. The most common ocular signs include myopia, ptosis, strabismus, and nasolacrimal duct obstructions. Levin et al described twenty-two patients with CdLS that had prevalence rates of sixty percent for myopia, fifty-nine percent for NLDO, forty-five percent for ptosis, twenty-two for strabismus, and about fifteen percent for nystagmus (Nallasamy et al, 2006). Other ocular findings include glaucoma, microcornea, and coloboma of the optic nerve. Figure 1 shown below features ocular structures that are affected by CdLS:
Cornelia de Lange Syndrome is characterized by distinct physical features that are easily observed and useful in its clinical diagnosis. These patients exhibit craniofacial features such as synophrys, long eyelashes, arched eyebrows, and microcephaly. Synophrys, or fused eyebrows, are present in approximately 98% of the patients (Jackson et al, 1993). Hypertrichosis, or excessive hair growth, is found in greater than eighty percent of patients with CdLS (Deardoff et al, 2006).

Prenatal onset of growth retardation affects over ninety-five percent of patients with CdLS. Upper limb abnormalities are more common lower limb defects and may be symmetric or asymmetric. These abnormalities range in severity from oligodactyly (fewer than normal fingers or toes) to micromelia (abnormally small or short limbs) (Deardoff et al, 2006). Figure 2, pictured below, is a patient diagnosed with CdLS who displays the classic facial features and limb abnormalities.
Systemic Characteristics of CdLS

Cornelia de Lange Syndrome is a disorder that presents with developmental anomalies in several parts of the body including the brain and heart. Cutis marmorata, a vascular anomaly in which the skin appears mottled, is noted in about sixty percent of cases (Deardoff et al, 2006).

Gastroesophageal reflux is one of the most common findings in patients with CdLS with incidences ranging from twenty-six to eighty-three percent (Sommer, 1993). Other gastrointestinal defects include pyloric stenosis and intestinal malrotation. Complications of gastroesophageal reflux such as esophagitis and aspiration can be avoided if it is diagnosed and treated during the neonatal period (Deardoff et al, 2006).

Sensorineural loss is found in approximately eighty-percent of children with
Cornelia de Lange Syndrome, with forty percent of these cases having profound hearing loss (Sataloff, 1990).

In 1998, Tsukahara et al noted that congenital heart disease was present in one-fourth of cases of CdLS. The most common cardiac anomalies seen are septal defects, pulmonary stenosis, and tetralogy of Fallot.

Severe to profound intellectual disability is observed in most cases of CdLS, with an average intelligence quotient of fifty-three (Kline et al, 1993). Cornelia de Lange Syndrome patients also demonstrate self-destructive behavior similar to autism. These patients tend to avoid physical contact or social situations.

**Differential Diagnosis**

Cornelia de Lange Syndrome shares similarities with other conditions, but can be differentiated through its distinct facial characteristics and autosomal dominant inheritance. Upon clinical presentation, CdLS can be similar to Fryns syndrome, Coffin-Siris syndrome, and fetal alcohol syndrome (FAS). Although Cornelia de Lange syndrome shares many of its characteristic facies with Fryns syndrome, CdLS has autosomal dominant inheritance whereas Fryns syndrome has autosomal recessive inheritance. Fetal alcohol syndrome physically resembles CdLS; however, the development and growth of limbs and speech are less affected with FAS.

**Treatment and Management**

Currently, there is not a treatment for Cornelia de Lange syndrome but rather treatment and management of its manifestations. With several ocular
findings noted in these patients, CdLS requires a complete ophthalmology evaluation. A dilated fundus examination must be performed to examine the retina and other intraocular structures. A motility examination is useful in documenting the presence of nystagmus and other extraocular muscle defects. To determine the patency and function of the tear ducts, a lacrimal system evaluation is indicated. The patient may be treated for refractive errors, strabismus, glaucoma, or ptosis, depending upon the severity of the condition. Aggressive treatment is indicated for nasolacrimal duct obstructions and may include lacrimal sac massages, probing, or a dacryocystorhinostomy (DCR).

**Conclusion**

Cornelia de Lange Syndrome is a congenital genetic developmental disorder that affects several systems in the body. It is caused by a mutation in one of three genes that produce proteins involved in growth and development; consequently, patients present with severe to profound developmental anomalies. Patients with CdLS share similar physical characteristics, especially in the head and face. Because there is no cure for CdLS, these patients require much care, treatment, and surveillance of the manifestations of the syndrome.
Bibliography

http://www.CdLSusa.org


Figure 1A: http://www.uveitis.org/images/Aqueous_flow.jpg

Figure 1B: http://img.tfd.com/ElMill/thumb/F0L-01-S2958.jpg

Figure1C:  

Figure 2: http://scielo.isciii.es/img/revistas/medicorpa/v12n6/07.htm20.jpg