

Cornelia de Lange syndrome

Also known as: de Lange syndrome, Brachmann-de Lange syndrome

Clinical Characteristics

The manifestations of Cornelia de Lange syndrome include characteristic craniofacial features, growth failure, developmental delay, limb abnormalities, and hirsutism. Audiologic, ophthalmologic, genitourinary, cardiovascular, and gastroesophageal issues are also common. Some individuals have been known to develop autistic-like behaviors. Cornelia de Lange syndrome is usually first suspected due to the recognizable craniofacial features, including: frontal head circumference below the 2nd percentile, synophrys, long & thick eyelashes, low-set posteriorly rotated ears, a broad nasal bridge, a long & smooth philtrum, a thin upper lip, a crescent-shaped mouth, a small jaw, small & widely-spaced teeth, and a high arched palate (clefted in about 30% of cases).

Cornelia de Lange Syndrome and Hearing Loss

Approximately 80% of individuals with Cornelia de Lange syndrome demonstrate sensorineural hearing loss. The severity varies, but about 40% are profoundly affected. Hearing loss is often secondary to stenosis of the external auditory canals.

Natural History

Cornelia de Lange syndrome has been diagnosed in both males and females, though it is slightly more likely for females to be affected. There is no apparent predilection for race or ethnicity. The prevalence of the syndrome is estimated to be between 1 in 10,000 and 1 in 100,000. There are "classic" and "mild" forms of the disorder.

Prenatal growth deficiency is found in over 95% of patients with classic Cornelia de Lange syndrome. Growth is persistently below the 5th percentile throughout life. About 25% of patients also have limb abnormalities, most often in the upper extremities. The facial manifestations are present at birth and change little over the course of a lifetime, though some features may become more obvious around 2-3 years of age. Gastroesophageal reflux and other gastrointestinal problems are often present at birth and may cause difficulties with feeding. Possible ophthalmologic issues include myopia and nystagmus. Approximately 25% of patients have congenital heart disease, including septal defects. Genitourinary abnormalities include cryptorchidism in 73% of males, hypoplastic genitalia, and renal abnormalities. Mild to profound mental retardation has been reported, with most individuals in the moderate range. Autistic-like behaviors such as self-injurious behaviors, social avoidance, and poor expressive communication are sometimes seen, most often when an individual is frustrated at their difficulties in communicating.

Life expectancy is normal if no major malformations occur. Causes of death include respiratory apnea, cardiac malformations, and gastrointestinal complications.

Genetics

The genes *NIPBL* (on chromosome 5) and *SMC1L1* (on the X chromosome) are known to be involved in Cornelia de Lange syndrome. The normal gene product, the delangin protein, is not well-understood, though it is known to help direct development before birth. Autosomal dominant and X-linked inheritance patterns have both been documented, but about 99% of cases are due to new mutations and no history of the syndrome in the family is seen. If parents are indeed unaffected, the recurrence risk for siblings is approximately 1.5% due to the possibility of mosaicism in the germ cells of the parents.

Management

The diagnosis of Cornelia de Lange syndrome is made clinically. Molecular genetic testing is available on a clinical basis. A mutation is found in about 50% of cases, more often in those with a milder phenotype. If a mutation is identified in an affected individual, prenatal testing is available.

As of right now, there are no standardized guidelines for management. Treatment protocols are available at CdLS World at www.cdls.org. Recommendations at the initial diagnosis include a gastrointestinal evaluation, the use of Cornelia de Lange syndrome-specific growth charts, radiographs of the upper extremities, an audiology evaluation, an ophthalmologic evaluation, an echocardiogram, a neurologic evaluation and EEG, a renal ultrasound, and a urologic evaluation for males with hypospadias and/or cryptorchidism.

Surveillance measures include annual gastrointestinal evaluation and growth monitoring, annual evaluation by a developmental pediatrician to identify appropriate interventions and education models, monitoring of any cardiac or renal abnormalities by specialists, and regular follow-up for audiological and ophthalmologic abnormalities.

Treatment for hearing loss is standard based on the type and severity of the loss. Treatment for gastrointestinal issues, particularly reflux, should be treated aggressively. Nutrition should be monitored carefully and the intervention of a nutritionist may be necessary. Special formulas or the placing of a gastrostomy tube could be indicated. Regular physical, occupational, and speech therapies may improve development.

Scheduling an appointment with a geneticist and/or genetic counselor should be considered.

Resources for Families

Statewide Genetics Program

Phone: 608-267-7148

Fax: 608-267-3824

Email: meyeram@dhfs.state.wi.us

Wisconsin First Step Hotline

Phone: 1-800-642-7837 voice/TTY

Website: www.mch-hotlines.org

Wisconsin Office for Deaf and Hard of Hearing

Phone: 1-608-266-3118 voice/TTY

Website: www.dhfs.state.wi.us/sensory

Regional Children and Youth with Special Health Care Needs Centers

Centers in Green Bay, Wausau, Milwaukee, Madison, and Chippewa Falls

Website: http://dfhs.wisconsin.gov/DPH_BFCH/cshcn/index.HTM

WI Chapter of Families for Hands & Voices

Phone: (920) 437-7370

Website: www.handsandvoices.org

Parent-to-Parent of Wisconsin

Phone: 1-888-266-0028

Email: rmathea@shsmh.org

Family Village online resource

Library Card Catalog of Disorders

www.familyvillage.wisc.edu

The Cornelia de Lange Syndrome Foundation, Inc.

302 W Main Street, #100

Avon, CT 06001

Phone: 1-860-676-8166 OR 1-800-223-8355

Web: www.cdlsusa.org

National Organization for Rare Disorders (NORD)

www.rarediseases.org