May 2018- Cornelia de Lange Syndrome Awareness Day

A note from the author—

Hello NCP friends! The NCP Health Ministry always aims to provide a variety of articles over the course of the year, from common health conditions, to preventative health topics, to the most recent health threats facing our community. However, every once in a while, I like to feature a health condition or topic that is more rare or unknown. This month, I came across a topic that even I, as a nurse, have never even heard of before: Cornelia de Lange Syndrome (aka CdLS). This month, learn with me and read more about this rare genetic condition!

What is CdLS Awareness Day?

National CdLS Awareness Day is observed the second Saturday of May each year in order to shed light on this often misdiagnosed, little-known genetic syndrome. Since CdLS (Cornelia de Lange Syndrome) is unfamiliar to most people, including professionals in the medical community, Awareness Day—celebrated since 1989—is an opportunity to educate all segments of the population about the syndrome.

Each year, parents, volunteers and others request official Awareness Day proclamations from governors and local leaders; hang awareness fliers in public places; make presentations to civic groups or health workers; write their local newspapers; and much more. In summary, it is a day dedicated to learning and encouraging people to be positively involved in the spread of more useful information about this disease.

The Origin of CdLS Awareness Day

Medical authorities named Cornelia de Lange Syndrome Awareness day after the rare congenital disease discovered by a Dutch pediatrician, Dr. Cornelia de Lange. She thoroughly observed and wrote extensively about CDLS in 1933. According to medical journals, CDLS is a multisystem developmental disorder. Although the genetic basis of this syndrome is still unclear, some medical practitioners believe that it is a result of a chromosome mutation.

Why Observe CdLS Awareness Day?

A child with CDLS, as a rule, fails to live past two years old because of multiple dysfunctions and growth retardation. Some of these include gastro-esophageal dysfunction, genitourinary anomalies and other body system failures. It is very difficult for family members and for the patient to function within society's norms given these conditions. The observation of Cornelia de Lange Awareness day can shed a light and bring to the surface the suffering endured by these people. It can encourage dialogue not only between medical personnel but also among the public on possible reasons why the syndrome exists and what we can do to prevent its occurrence. It is important for us to be aware of this syndrome and learn more about it. It will give us an understanding of the extent of the effect CDLS has on people diagnosed with it; therefore we can empathize with their plight.

The Goal of CdLS Awareness Day

When someone is in a dire situation, it is much easier to just to close our eyes on their sufferings thinking that it does not affect us. However, that does not change the fact that those people are part of our world. We are all connected one way or another. Cornelia de Lange Syndrome Awareness Day should move us to be more proactive. Observing the awareness day should make us seek creative ways on how we can be of better service to people suffering with the illness. However long or short the life of a person diagnosed with the syndrome, let us remember that our situation is far better than his or hers.

The Prevalence of Cornelia de Lange Syndrome

Cornelia de Lange Syndrome (CdLS) is a genetic disorder present from birth, but not always diagnosed at birth. It causes a range of physical, cognitive and medical challenges and affects both genders equally. CdLS does not discriminate—it's seen in all races and ethnic backgrounds. The occurrence of CdLS is estimated to be 1 in 10,000 live births. More than 400 cases have been reported in the medical literature, including affected individuals within several families (kindreds). Multiple affected siblings have been reported in some families. It is estimated that there is a 1-2 % rate of recurrence within affected families. An estimated 20,000 men, women and children have CdLS but remain undiagnosed and/or without any support services.

What is CdLS?

Cornelia de Lange syndrome (CdLS) is a syndrome of multiple congenital anomalies characterized by a distinctive facial appearance, prenatal and postnatal growth deficiency, feeding difficulties, psychomotor delay, behavioral problems, and associated malformations that mainly involve the upper extremities. Cornelia de Lange first described it as a distinct syndrome in 1933, although Brachmann had described a child with similar features in 1916. Diagnosing classic cases of Cornelia de Lange syndrome is usually straightforward; however, diagnosing mild cases may be challenging, even for an experienced clinician.

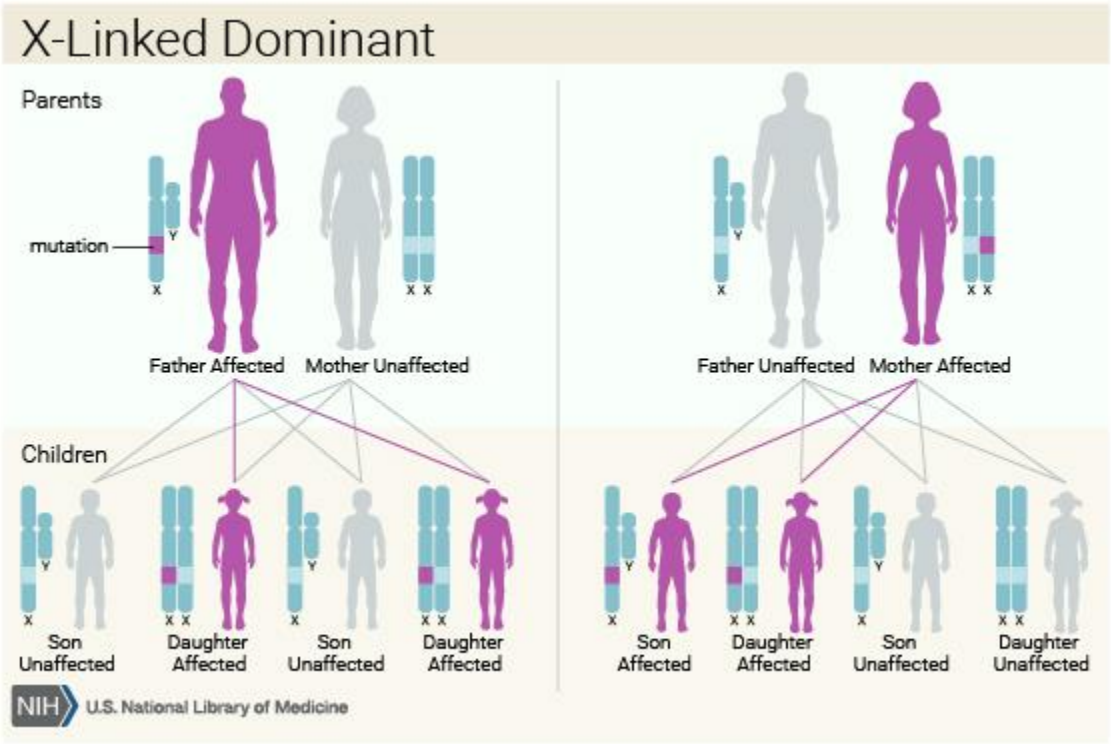
The Genetic Link

CdLS can be inherited as an autosomal dominant condition or an X-linked condition. Five genes have been found to be associated with CdLS including the *NIPBL* gene on chromosome 5, the *SMC1A* gene on the X chromosome, the *SMC3* gene on chromosome 10, the *Rad21* gene on chromosome 8 and the *HDAC8* gene on the X chromosome. Approximately 60% of those affected have a NIPBL gene mutation and a small percentage (about 10%) have mutations in the other genes. Most affected individuals have an abnormal gene as a result of a new gene mutation and do not have an affected parent. Other genes may be found to be associated with CdLS in the future.

Dominant genetic disorders occur when only a single copy of an abnormal gene is necessary to cause a particular disease. The abnormal gene can be inherited from either parent or can be the result of a new mutation (gene change) in the affected individual. The risk of passing the abnormal gene from affected parent to offspring is 50% for each pregnancy. The risk is the same for males and females.

X-linked genetic disorders are conditions caused by an abnormal gene on the X chromosome and occur mostly in males. Females that have a disease gene present on one of their X chromosomes are carriers for that disorder. Carrier females usually do not display symptoms because females have two X chromosomes and one is inactivated so that the genes on that chromosome are nonfunctioning. It is often the X chromosome with the abnormal gene that is inactivated. However, in CdLS, because the gene change is likely dominant over the corresponding gene on the X chromosomes, females also often show similar findings as males.

Males have one X chromosome that is inherited from their mother and if a male inherits an X chromosome that contains a disease gene he will develop the disease. Female carriers of an X-linked disorder have a 25% chance with each pregnancy to have a carrier daughter like themselves, a 25% chance to have a non-carrier daughter, a 25% chance to have a son affected with the disease and a 25% chance to have an unaffected son. Males with X-linked disorders pass the disease gene to all of their daughters who will be carriers. A male cannot pass an X-linked gene to his sons because males always pass their Y chromosome instead of their X chromosome to male offspring.



Signs and Symptoms of CdLS

CdLS is a very rare disorder characterized by growth delays; distinctive facial features; malformations of the hands, feet, arms, and/or legs (limb anomalies); other physical abnormalities; intellectual disability; and/or developmental delays. The range and severity of symptoms and physical characteristics may vary greatly from person to person.

A child with this syndrome typically shows the following characteristics:

- Has growth or developmental retardation
- Low birth weight
- Experiences difficulty feeding and breathing
- Has a small head, short neck, and is smaller in stature than normal
- Very bushy arms and legs or with too much body hair (hirsutism)

Children with CDLS remarkably resemble one another. A typical facial characteristic includes thin eyebrows that frequently join in the middle, deformed upper limbs, and a crescent shaped mouth. Many medical journals agree that CDLS symptoms may or may not be discernible during birth. It is advisable to seek a qualified physician to do a thorough examination before concluding that a child has the unusual disease.

More Signs and Symptoms

As stated above, many signs and symptoms of CdLS vary greatly from person to person. However, the information below regarding other signs and symptoms of CdLS has been documented by medical professionals and may aid in proper diagnosis.

1. Individuals with CdLS exhibit abnormal growth delays that affect both weight and linear growth before and after birth (prenatal and postnatal growth retardation). Most affected infants may have a low birth weight and may fail to gain weight or

grow at the expected rate (failure to thrive). CdLS growth charts are available to compare growth to other affected individuals. Individuals may experience feeding, chewing, and swallowing difficulties during the first several months/years of life.

2. Many affected infants may frequently “spit up” food that has already been swallowed (regurgitation) and may experience episodes of severe, forceful vomiting (projectile vomiting). Infants with CdLS may also demonstrate abnormally increased muscle tone (hypertonicity) and have an unusual, low-pitched, growling cry.

3. Individuals with CdLS also have distinctive features of the head and facial (craniofacial) area including an abnormally small head (microcephaly) that may also be unusually short (brachycephaly); a short, thick neck; a low hairline; a small, broad, upturned nose with nostrils that tip upwards (anteverted nares); neat, arched eyebrows that grow together (synophrys); long, curly eyelashes; and/or excessive hair growth on various areas of the body (hypertrichosis). Additional features may include thin, downturned lips; an abnormally long vertical gap between the upper lip (philtrum) and the nose; an abnormally small, underdeveloped jaw (micrognathia); late-erupting, widely-spaced, unusually small teeth; and low-set ears. In some cases, affected infants may also exhibit incomplete closure of the roof of the mouth (cleft palate), a hidden incomplete closure (submucous cleft palate) and/or a highly arched palate.

4. In most infants with CdLS, the hands and feet are small for their size. In addition, affected individuals may have short fingers that become smaller and thinner toward the ends (tapered fingers), fifth fingers that are permanently curved toward the ring finger (clinodactyly), and/or, in some people, absence of one or more fingers (oligodactyly). The thumbs may be abnormally positioned (i.e., proximally placed) and the arms may be permanently bent or flexed at the elbows due to bone fusions. In addition, in many cases, affected individuals may demonstrate underdevelopment (hypoplasia) of some of the bones of the fingers

and toes, and the second and third toes are often abnormally fused or webbed (syndactyly). Some affected infants may also have, in rare cases, fingers, hands, and forearms which are missing. In individuals with CdLS, upper limb abnormalities may involve one side (unilateral) or both sides (bilateral) of the body. If bilateral limb malformations are present, the abnormalities on one side of the body may be completely different from those on the other side (asymmetrical). Although the feet are small, only in extremely rare cases are there absent bones in the feet or lower legs.

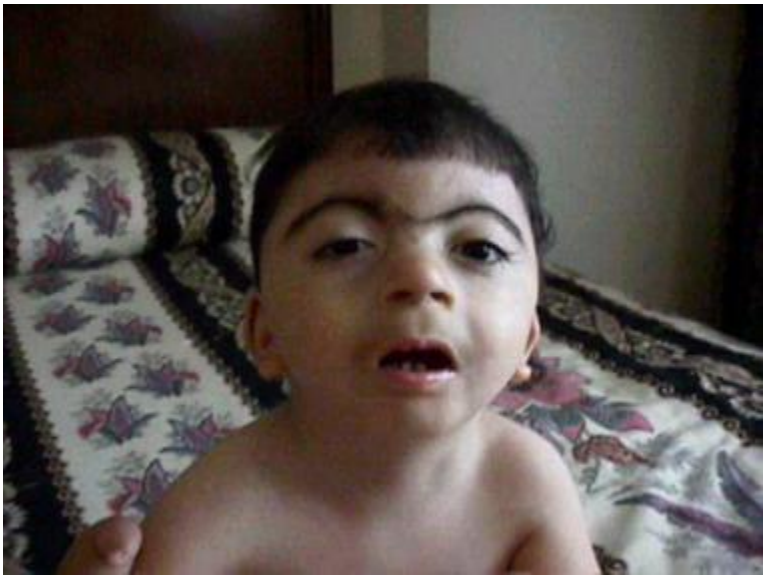
5. Individuals with CdLS also demonstrate delayed bone age (retarded osseous maturation). In addition, affected individuals may remain low in weight and exhibit abnormally short stature (prenatal and postnatal growth retardation), failure to thrive during infancy, delayed bone age, and/or other abnormalities. Many individuals with CdLS also exhibit additional skeletal abnormalities. These may include a deformity of the hip (coxa valga), a short breastbone (sternum), and/or abnormally thin ribs.

6. Many infants and children with CdLS may exhibit delays in the acquisition of skills requiring the coordination of mental and muscular activity (psychomotor retardation), have mild to severe intellectual disability, and/or demonstrate behavioral problems (e.g., episodes of biting, screaming, hitting themselves, etc.). In addition, although affected children have decreased facial expression based on emotion, they appear to respond positively to certain stimuli (e.g., fast movements). A CdLS developmental chart is available to compare milestones.

7. Many children with CdLS also have hearing impairment as well as abnormal speech development. Middle ear infections (otitis media), which sometimes occur chronically with an accumulation of sticky fluid (otitis media with effusion or glue ear), are common. Younger children may have difficulty speaking (dysphonia), while older children may have abnormally hoarse speech.

8. Many individuals with CdLS also exhibit additional physical abnormalities. In many cases, the skin may appear “marbled” (cutis marmorata), and the skin above the eyes, mouth, and nose may have an unusual bluish tone. In addition, many affected individuals demonstrate irregularities in the skin ridge patterns on the palms of the hands (dermatoglyphics). As mentioned earlier, most affected individuals may exhibit excessive hair growth (hypertrichosis) on various areas of the body including the ears. Hair may also tend to appear on the lower back, limbs, and/or other areas of the body.

9. Many individuals with CdLS also have various abnormalities of the gastrointestinal system including gastroesophageal reflux, a condition in which the acidic contents of the stomach flow upward into the lower esophagus; inflammation of the lining of the esophagus (esophagitis); and/or narrowing of the esophagus (esophageal stenosis). In addition, affected individuals may have abnormal twisting (malrotation) of the intestines, potentially causing intestinal obstruction (volvulus). In some children, the bands of muscle fibers (pyloric sphincter) at the junction between the stomach and small intestine (pyloric stenosis) may become abnormally narrowed (stenosis) in infancy, resulting in obstruction of the normal flow of stomach contents into the small intestine. In addition, some individuals with CdLS may also have protrusion of portions of the large intestine through an abnormal opening in musculature lining the abdominal cavity in the area of the groin (inguinal hernia) and/or part of the stomach through an abnormal opening where the esophagus passes through the diaphragm (hiatal hernia). In some individuals with CdLS, certain gastrointestinal abnormalities may lead to intestinal obstruction, potentially causing serious or life-threatening complications if left untreated.



10. Some individuals with CdLS may also have malformations of the genitourinary tract. In affected males, such abnormalities may include underdevelopment (hypoplasia) of the genitals, failure of one or both of the testes to descend into the scrotum (cryptorchidism), and/or abnormal placement of the urinary opening

(urinary meatus) on the underside of the penis (hypospadias). Affected females may have abnormal development of the uterus (e.g., bicornate or septate uterus), and menstruation may be irregular.

11. Many children with CdLS have additional physical abnormalities including various heart (cardiac) abnormalities. Some affected individuals may also have an increased susceptibility to repeated respiratory infections, eye abnormalities such as nearsightedness (myopia), rapid, involuntary eye movements (nystagmus), and/or abnormal drooping of the upper eyelid(s) (ptosis). Some infants and children with CdLS may also experience episodes of uncontrolled electrical disturbances in the brain (seizures).

Diagnosing Cornelia de Lange Syndrome

Sometimes a diagnosis of CdLS may be suspected before birth (prenatally) through the use of ultrasound imaging. During such testing, reflected sound waves create an image of the fetus that may reveal certain abnormalities characteristic of CdLS such as retarded growth, limb abnormalities, facial anomalies and/or organ malformations.

Most children with CdLS are diagnosed clinically after birth or in childhood based upon a thorough clinical evaluation and identification of characteristic physical findings. A diagnosis of CdLS should be considered in children who exhibit certain distinctive facial features in association with limb anomalies, prenatal and postnatal growth retardation, and intellectual disability. Diagnosis may be more difficult if symptoms and physical characteristics associated with the disorder are very mild. Molecular genetic testing for mutations in the five genes associated with CdLS is available to confirm the diagnosis and may be particularly helpful when the physical features are mild or unusual. Prenatal diagnosis is available if a specific *NIPBL, SMC1A, SMC3, Rad21* or *HDAC8* gene mutation has been identified.

Clinical evaluation to identify such characteristic physical findings focuses on the following associated symptoms:

- Delays in physical development before and after birth (prenatal and postnatal growth retardation)
- Characteristic abnormalities of the head and facial (craniofacial) area, resulting in a distinctive facial appearance

- Malformations of the hands and arms (upper limbs)
- Mild to severe intellectual disability.
- Unusually small, short head (microbrachycephaly)
- A prominent vertical groove between the upper lip and nose (philtrum)
- A depressed nasal bridge
- Upturned nostrils (anteverted nares)
- Protruding upper jaw (maxillary prognathism) with small chin (micrognathia)
- Thin, downturned lips
- Low-set ears
- Arched, well-defined eyebrows that grow together across the base of the nose (synophrys)
- Unusually low hairline on the forehead and the back of the neck
- Curly, unusually long eyelashes.
- Unusually small hands and feet
- Inward deviation (clinodactyly) of the fifth fingers
- Webbing (syndactyly) of certain toes
- Less commonly, there may be absence of the forearms, hands, and fingers

Infants with CdLS may also have:

- Feeding and breathing difficulties
- An increased susceptibility to respiratory infections
- A low-pitched "growling" cry and low voice
- Heart defects
- Delayed skeletal maturation
- Hearing loss

Treating Cornelia de Lange Syndrome

The treatment of CdLS is directed toward the specific symptoms that are apparent in each individual. Treatment may require the efforts of a team of specialists working together to systematically and comprehensively plan an affected child's treatment. Such specialists may include pediatricians; geneticists; surgeons; specialists who diagnose and treat skeletal disorders (orthopedists); plastic surgeons; orthopedic surgeons; specialists who diagnose and treat abnormalities of the digestive system (gastroenterologists), disorders of the urinary tract (urologists), and abnormalities of the ears, nose, and throat (otolaryngologists); pediatric heart specialists (cardiologists); dental specialists; speech pathologists; specialists who assess and treat hearing problems (audiologists); eye specialists; physical and occupational therapists; and/or other health care professionals.

Affected infants and children may be closely monitored for certain abnormalities potentially associated with CdLS (e.g., potential intestinal obstruction due to gastrointestinal abnormalities, cardiac defects, gastroesophageal reflux, glue ear, and/or susceptibility to respiratory infections) to ensure early detection and prompt treatment.

Specific therapies for the treatment of CdLS are symptomatic and supportive. In some children, surgery may be performed to help correct cleft palate, cardiac defects and/or diaphragmatic hernias. Plastic surgery may be helpful in reducing excessive hair. Some gastrointestinal, genitourinary, and/or cardiac malformations may be treated with certain medications, surgical intervention, and/or other techniques. The surgical procedures performed will depend upon the location and severity of the anatomical abnormalities and their associated symptoms. Respiratory infections may be treated with antibiotic drug therapy and/or other medications that may help fight infection.

Various orthopedic techniques may be used to help treat limb deformities. Hearing aids may be beneficial in some children. Treatment with anticonvulsant medications may help prevent, reduce, or control seizures in some affected children.

Early intervention is important in ensuring that children with CdLS reach their highest potential. Services that may be beneficial include special remedial education, vocational training, speech therapy, and/or other medical and/or social services.

Genetic counseling is recommended for affected individuals and their families. Other treatment is symptomatic and supportive.

Resources
http://www.cdlsusa.org/what-is-cdls/
https://rarediseases.org/rare-diseases/cornelia-de-lange-syndrome/
http://www.chop.edu/centers-programs/center-cornelia-de-lange-syndrome-and-related-diagnoses

https://emedicine.medscape.com/article/942792-overview
http://www.cdlsusa.org/what-we-do/cdls-awareness.htm
https://www.consumerhealthdigest.com/health-awareness/cornelia-de-lange-syndrome-awareness-day.html
https://nationaldaycalendar.com/cornelia-de-lange-syndrome-awareness-day-second-saturday-in-may/