

Part 1

A Diagnosis of CdLS



How Did the Syndrome Get Its Name?

The syndrome is named after Dr. Cornelia de Lange, a Dutch pediatrician who wrote a paper in 1933 describing two children with similar features. Born in Alkmaar, Holland in 1871, she was a pioneering woman in medicine and obtained her education over the objections of her father. She would become a classical scholar and a defining force in pediatrics in the first half of the twentieth century.

Graduating from medical school in Amsterdam in 1897, she worked as a general practitioner before specializing in pediatrics. She is remembered as a quiet and friendly woman who recognized that pediatrics needed to be a specialty in its own right and wrote a book (*The Mental and Physical Education of the Child*) on childcare that was the standard for parents of the early twentieth century. Her success as a pediatrician was crowned by her appointment as the first Professor of Pediatrics at Amsterdam University.



Dr. de Lange endured the German occupation of World War II and remained faithful to her patients despite being ill. She died in 1950. For her lifetime of accomplishment she received a Knighthood from the Dutch government.

Some medical publications and historians call this syndrome “Brachmann de Lange Syndrome” after Dr. W. Brachmann because he described a similar patient earlier in 1916. The Foundation chose to name itself after Dr. Cornelia de Lange because, by 1981 when the foundation was incorporated, caregivers were using the acronym “CdLS,” not “BdLS” when referring to this diagnosis.

Getting the Diagnosis

It is important to remember that a person is a person first, and the diagnosis is secondary. Because of the wide variation within this syndrome and the lack of a single, defining characteristic to confirm the diagnosis, the general label of Cornelia de Lange Syndrome (CdLS) may or may not be helpful in understanding how a child will develop. Every person is unique and decisions regarding care should be made on the basis of what is best for that individual.

The diagnosis of Cornelia de Lange syndrome can provide additional information to consider as a person with CdLS grows and develops. Having a diagnosis may help to understand why a child is delayed or why she may need to have therapy or a medical consultation. A confirmed diagnosis may also be of assistance in obtaining early intervention services. What is important is that an accurate diagnosis

In May of 1987 our son was born. Less than 30 minutes from the moment of birth, we were told he had a syndrome. Within hours the diagnosis was made: Michael had Cornelia de Lange Syndrome. At a time when my husband and I were supposed to be feeling the excitement and joy of the birth of a new child, our world was instead shattered. In a few short minutes, nine months of plans and dreams were destroyed. We had no warning, no preparation. Suddenly we were the parents of a little boy who needed us very much.

I work with several of your families in my genetics practice. One of the mothers told me that she and her husband spent their first session with me in confusion. The impact of receiving the diagnosis really blocked them from absorbing all the information I had offered. Since then, I always schedule a follow-up appointment to further discuss the child and to answer all the questions that occur after the initial shock wears off.



be made as early as possible and that decisions are based on what is presently known about ways to help people with CdLS.

Whether a child is diagnosed within moments of birth or years afterward, receiving a diagnosis of Cornelia de Lange Syndrome can be overwhelming. Once diagnosed, a child is no longer just “Maria” or “Robert,” she or he has an additional label, which is long, difficult to say, and initially, very confusing.

The reaction of caregivers to this information is as individual as the people themselves. The news often begins a lifelong process of challenging and re-challenging their feelings, thoughts, actions and beliefs about the nature and fairness of the world. New caregivers often find comfort in talking to one of the Foundation’s social workers who may refer them to professionals specializing in the syndrome or other caregivers who are willing to provide support.

I knew in my gut something was wrong. The doctor finally listened and confirmed my suspicions. He sent me to a geneticist the very next day. By then it was a relief to find that my child's difference had a name and that there were other people with whom I could share my worries.



Grief

It is important to remember that the grieving process is normal and to be expected in the event of a birth of a child with disabilities. However, even though parents and other family members may experience feelings of anger, guilt, denial, and sadness, these feelings do not necessarily interfere with the ability to love someone with the syndrome. Whether you try to help grief along or refuse to acknowledge its existence, it will run its course. It probably won’t happen quickly, and it is often painful, but it will happen. Just as a child grows and changes, so will his or her family. Although the old dreams may not fit anymore, new dreams will take their place.

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For me, being a parent meant making sure my child would be protected from all the danger and harm . My definition of motherhood did not include taking my child to therapies that might hurt.

Members of the Scientific Advisory Council (SAC) have detailed the emotional responses that grieving parents can anticipate from themselves and family members upon hearing news of this diagnosis:

The first response is often *shock*. No one is ever ready for the news that her or his child has a disability -- no matter how the news is given. It is the realization of every parent's worst fear -- "what if something is wrong with my baby?" Shock can be protective, however, for it can insulate a person from the trauma in learning of a child's disability and the painful feelings that occur early on.

Another emotion that is common for parents to experience is *denial*. Like the feeling of shock, denial blunts the initial impact of the news and gives people the time needed to get themselves together. It is common for parents to express disbelief about a diagnosis, or even to harbor some hope that the doctor will "make the baby normal again." Some families will pursue a long series of medical opinions in an attempt to dispel the notion that their baby does have a disability.

Anger and other feelings such as resentment, irritability and disappointment are very common. They may result from feelings of helplessness, frustration and loss of control. They are a very normal part of grieving, along with feelings of *guilt* -- beliefs that family members themselves were somehow responsible for the disability. Sharing thoughts with others can help ease feelings of guilt and anger. Families should remember that there is no known cause for CdLS and that nothing could have been done to prevent its occurrence.

Sadness is also very common, and can manifest itself in crying spells, difficulty with sleep, changes in appetite or decreased interest in activities. Parents of children with a disability often feel emotionally isolated from each other, from family, and from friends. Some people may even experience lifelong feelings of sadness, called "chronic sorrow," over the birth of a child with a disability.

Men and women have different grieving styles. As a result, partners may feel unable to lean on each other for strength and support, leading to further sadness and isolation. Partners need to respect each other's way of coping. There will be sadness, but there will also be joy. There will be many difficult decisions to make, but they need not be faced alone. The CdLS Foundation has many families, friends and professionals ready to offer information, support and encouragement along the way.

What is CdLS?

All parents wonder – and worry just a little – about what their baby will look like and whether he or she will be healthy. At birth, all babies are routinely examined for the indicators of good health, including length, weight, muscle tone, reflexes, heartbeat and other vital signs, as well as the number of fingers and toes. Sometimes a doctor may be concerned with the physical appearance of a newborn, which – although it may not appear “abnormal” – may be a clue to an underlying medical problem. Pediatric medical specialists, such as a clinical geneticist, neurologist, cardiologist and/or gastroenterologist may be consulted to determine if further evaluation is needed.

CdLS – a disease, disorder or syndrome?

Most people who talk about CdLS are confused about whether it is a syndrome, disease or disorder. The word “syndrome” literally means “running together.” When professionals use the word “syndrome,” they are referring to two or more characteristics or medical problems that consistently occur together -- a diagnosis is made by adding up all the signs, such as long eyelashes, short upturned nose, small head, etc.

While CdLS is not a disease itself, the syndrome may result in a specific “disease” or “disorder,” words that are generally used to describe a single abnormal function of a body part, organ or system. For example, pneumonia (an inflammation of lung tissue) is a disease or disorder that someone with CdLS could develop as a result of the syndrome.

At present, there is no single criteria which definitely establishes a diagnosis of Cornelia de Lange Syndrome. With CdLS, several physical, developmental and

When people ask me the why of CdLS I used to get very frustrated at my inability to produce an easy answer. Finally I started saying that CdLS just happens. There is no known cause and nothing anyone could have done to prevent it. I know people don't like this answer because they are afraid that it could happen to them or someone they care about.

The doctor came to see us shortly after our daughter's admission to the hospital and said that her head was too small. After about a week or so she was diagnosed with CdLS. It was so hard for us to believe our baby was not perfect. But at least we finally knew after six months of worrying why she wasn't gaining weight.

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medical features generally appear together, **although not all individuals with the syndrome exhibit all of the features described.** Diagnosis depends on the presence of a combination of characteristics (see next section for these characteristics), many of these traits appearing in varying degrees. In some cases these characteristics may not be present or may be so mild that they will be recognized only when observed by a trained geneticist or other professional familiar with the syndrome.



When the features are subtle and not obvious to family and friends, it is often hard for parents to believe their healthy-looking baby has such a potentially serious condition. Even more confusing is the fact that many features found in children with CdLS can also be seen in children who do not have the syndrome. It is the combination of features in an individual that may indicate that CdLS is present.

CdLS does not discriminate, consequently, children with CdLS are born everywhere in the world, regardless of race, age of parents, religion, or socioeconomic status. This syndrome displays no predictable pattern, affecting children throughout the birthorder (first, last, or middle child) and both sexes equally.

Incidence of CdLS

At present it is estimated that the incidence of CdLS is between 1:10,000 and 1:30,000 live births.

The Foundation presently serves more than 2,000 people with CdLS within the United States (and another 1,500 worldwide) and believes that there are tens of thousands more who live undiagnosed and unaware of the services available. The organization's mission is to reach as many people as possible and expand programs of family support and awareness to meet their needs. New families contact the Foundation office daily and the additional information gained from every family helps answer the incidence question – and every other question – much more accurately.

When our son was born 30 years ago, we were told there were only 18 known cases in the world. We have been amazed to learn about the thousands of people with CdLS worldwide. At the conference last year, we felt we had the opportunity to see over 100 other children and finally realized that we were not alone.

Arriving at a Diagnosis

CdLS is a congenital syndrome, meaning that it is present from birth and that most of the signs and symptoms may be recognized at birth or shortly thereafter. However, if the features are subtle and not readily apparent to family, friends or members of the medical profession, the diagnosis of CdLS may not be established at birth. The variability of characteristics presents a difficult challenge for geneticists not familiar with this syndrome. Usually the diagnosis is made during the first few days or months of life, but sometimes it is not confirmed until a child is three years or older.

Some children tend to “grow into” their features, hindering early diagnosis. **Although most children with CdLS strongly resemble one another, it is important to remember that as much as one child may look like another child with the syndrome, she or he may also resemble members of her or his own family.** Moreover, other syndromes with similar characteristics to CdLS may require a physician’s consideration before a diagnosis of CdLS can be made. *Remember that a child need not demonstrate each and every sign or symptom to receive the diagnosis.*

Over the last two decades, SAC professionals have collected medical records and information on hundreds of people with CdLS, ranging from newborn to age 70. Members of the SAC continue to conduct research into both the cause and manifestations of the syndrome.

We don't know what to think. The doctors tell us Jeff has CdLS. He is small, but eats well and is gaining weight. My husband's parents think Jeff looks like his Daddy and others on their side. Yet we can see some of the features that our doctor pointed out to us in a photo of another child with the syndrome. It is just so confusing and overwhelming right now.

It took me five and a half years to have Eddie diagnosed. My family doesn't understand why I was so happy just to know what he has. They don't understand how difficult my life has been worrying about what I did or did not do to cause him to be like he is. It is worth so much to finally know.



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Because of the SAC's efforts and that of others, we are able to share with you much of the scientific information contained in this book, including the following characteristics of CdLS:

MAJOR CHARACTERISTICS:

An individual may have many of the following traits or only a select few. Geneticists establish the diagnosis after evaluating all the criteria.

1) **Birth Weight, Growth, and Head Size.** The average birth weight for babies with CdLS is five pounds and one ounce, with birth weights reported ranging from one pound and two ounces to ten pounds. The average birth length is approximately 18 inches.

We met a young mother at the hospital. Her son was very sick and had a lot of problems. She said the doctor told her all the things that were wrong with her son and all the things he would never do. Then she said, But you know, the doctor never said that he would make me smile. I don't know her name, but I think of her and her son every time my daughter makes me smile.

Those with CdLS are often short of stature and below average in weight when compared to others their age. Likewise, small head size (microcephaly) is a feature commonly associated with the syndrome.

Although it appears that babies born under five pounds have "a higher incidence of major upper limb malformations" and start walking at a later age, there is presently **no scientific data to indicate that all babies with a low birth weight are more profoundly affected.** Likewise, babies who weigh more than five pounds at birth may not be less affected than those who weigh less than five pounds. In other words, there is no firm evidence that birth weight is the only indication of a child's prognosis.

When our daughter was diagnosed, all I could see was her syndrome the eyebrows, the nose, the mouth, the hands, the feet the endless list of anomalies that added up to CdLS. I didn't marvel at her perfection as I had done with my older daughter. In fact, I hurried through her bath and rushed to put her clothes on. But as she grew, her own personality overshadowed the syndrome. She is a delightful little girl with a great sense of humor. At first I felt guilty because it wasn't the same instant bond we had experienced with our first child, but now I know it was just part of the adjustment process and that she will always hold a very special place in our hearts.

We keep asking ourselves, Why? Why did this have to happen to our baby? The doctors did chromosome tests on all three of us and the results were perfect. It's hard, but I guess we will just have to wait for an answer.

2) **Developmental Delays (mental retardation).** The vast majority of children diagnosed as having CdLS are mentally retarded, the degree ranging from mild to severe with reported IQ's from 30 to 85. The average IQ is 53.* These cognitive deficits result in learning disabilities and often, severe language delays. Although mental retardation is

generally considered essential for a diagnosis of CdLS, there have been extremely rare instances of people with CdLS with borderline to normal intelligence.

*Many children born after 1980 are reported to have higher IQ scores, the reasons for this increase need further study. Early intervention services as well as the increase in accurate diagnosis of children who are more mildly affected certainly play an important role in explaining these results.

3) **Behavior.** People with CdLS can exhibit a number of behavioral problems such as self-injury (head-banging, hand biting, etc.), compulsive repetition, or other autistic-like behaviors. Attention deficit disorder and hyperactivity have also been noted.

SECONDARY CHARACTERISTICS:

1) **Facial Features.** Thin eyebrows which often meet at the midline (synophrys), long eyelashes, short upturned nose, thin downturned lips, low-set ears and high-arched palate or cleft palate.

2) **Hirsutism.** Excessive body hair.

3) **Limb Differences.** Small hands and feet, incurved fifth fingers (clinodactyl), partial joining of the second and third toes, proximally placed thumbs, and limb abnormalities, including missing portions of limbs – usually fingers, hands or forearms.

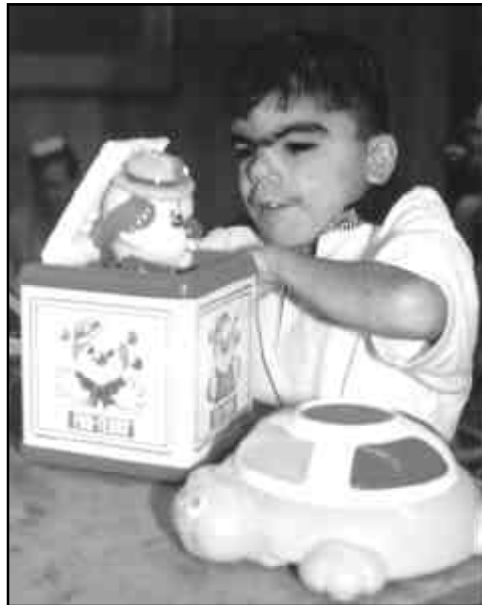
4) **Neurosensory System Abnormalities.** Hearing loss and eye ailments such as blepharitis (inflammation of eyelid), faulty or nonexistent tear ducts, ptosis (droopy lids), and extreme nearsightedness.

Other medical concerns may include gastroesophageal reflux and feeding difficulties, seizures, heart defects, ear, nose and throat problems, bowel abnormalities, undescended testes, and purplish discoloration of the skin (cutis marmorata).

What Causes CdLS?

After the birth of a child with CdLS, parents (and everyone else!) naturally reflect on the pregnancy and try to find a cause for the syndrome. At present, the cause of CdLS is not clearly known, although it is suspected that a gene or gene region may be responsible for its occurrence. If a gene is involved, it is most likely a rare and random mutation not passed directly from parent to child. There is very little likelihood that a child's syndrome resulted from anything done or not done during pregnancy.

Exposure to substances like alcohol, cigarettes, aspirin, caffeine, clinical x-rays and pesticides have been investigated and are not related to CdLS.



Although the location of the gene believed to cause CdLS is not known, there are many ongoing research projects that hope to locate the genetic marker. Several members of the SAC as well as other interested researchers are working together to find this marker. They hope to gain a better understanding of why this syndrome varies so widely from one individual to another and what can be done to improve the quality of life for people with this syndrome.

I want to understand why this happened to our daughter. Finding the cause of CdLS will help me provide the answer to the question of Why that everyone always asks. I m not sure it will help or change Christy who knows? Maybe she will not have the diagnosis, but what then? I only know that if there is a chance it will help her or someone else I want to support that effort.

Once the genetic marker is located, researchers can attempt to replace, correct or add a normal gene (gene therapy) for the purpose of alleviating or reducing some of the symptoms that are present in this syndrome. The location of the gene, its functions, and what can be done to help people with this gene are all questions currently being explored. Large numbers of parents have volunteered to have their blood and that of their children collected, analyzed and stored for these research purposes.

Recurrence/Prenatal Testing

Since individuals with CdLS seldom have children of their own, this gene is almost never passed on to the next generation. There have, however, been individuals mildly affected by the syndrome that have become parents to children also affected by the syndrome. There have also been cases where more than one child with CdLS has been born to a parent who does not appear to have CdLS.

Despite these examples, recurrence of CdLS within a family is extremely rare. Research indicates that the maximum recurrence rate of CdLS within a family is less than one percent (six-tenths of one percent).

Parents of a child with CdLS who are considering adding to their family and have questions about doing so, are strongly advised to seek genetic counseling. And, while there is no definitive prenatal test which can accurately predict the birth of a child with CdLS, other tools can help resolve some

of the uncertainty parents may feel during a pregnancy. One such tool is the Pregnancy Associated Plasma Protein - A (PAPP-A) test, a blood test taken during pregnancy that might signal an increased or decreased risk for the fetus to have CdLS. The PAPP-A test can be run on a mother's blood serum taken at various stages of her pregnancy. This test is not routinely done during standard prenatal care, thus one must ask that this specific test be done.

It is important to understand that the PAPP-A test estimates an increase or decrease of **risk** and **is not a diagnostic test**. If it suggests an increase of risk then it could be followed by some more definitive test, such as a stringent and targeted analysis of ultrasound features of the fetus that might enable one to confirm or deny the diagnosis. For families with anxiety over successive pregnancies when there is already a child with CdLS in the family, this could be helpful for alleviating their worries.

*From one mother to another who has a child with CdLS and is expecting again:
My baby is due in about two weeks, and at times this pregnancy has seemed like nine years, not nine months. I wish I was a kangaroo and could peek inside at the little one kicking at me to see two hands, two feet, etc. Is it a boy or a girl? But even if it has no hands or feet, I know I will love it. I wish the best for you, your husband and your son, no matter what you decide. The night I wrote this letter, I was admitted to the hospital and delivered a healthy boy. He was nine pounds, four ounces and twenty-one inches long. He is fat, sassy and healthy just like his Mom, and we feel very blessed.*

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If prenatal testing is being considered, it is important that parents discuss the benefits and risks of all procedures with a genetic counselor who will have the latest available information on these tests.

By the time you read this guide, there may be a test for CdLS available before and after birth. If such a test becomes available it is believed that not all people who are presently diagnosed with CdLS will have the genetic marker. However, the Foundation has expanded its mission to include those individuals with “similar characteristics” so that no person will be left alone should their diagnosis not be confirmed by a genetic test.

