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Review Article

Cornelia de Lange Syndrome: A Chronicle Review

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ABSTRACT

Cornelia de Lange disorder (CdLS) may be an intrinsic condition stamped by a characteristic facial appearance, pre-birth and postnatal development lacking, eating challenges, psychomotor delay, behavioral clutters, and concomitant upper limit distortions. W. Brachmann archived the primary case of CdLS in 1916, taken after Cornelia de Lange, a Dutch pediatrician, in 1933, after whom the clutter was named. In any case, not each individual with CdLS has the normal phenotype and can show in an assortment of ways, extending from gentle to severe and with shifting degrees of confront and appendage inclusion. The essential instrument behind CdLS has been hypothesized to be dysregulated quality expression. Surgery may be used to treat diaphragmatic hernias, heart anomalies, and/or cleft sense of taste in a few children. Over-the-top hair development could be decreased with plastic surgery.

Keywords: Cornelia de Lange syndrome, Brachmann-de Lange syndrome, Craniofacial, Synophrys, Micrognathia.

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INTRODUCTION

Cornelia de Lange disorder (CdLS) may be an intrinsic condition stamped by a characteristic facial appearance, pre-birth and postnatal development inadequate, eating challenges, psychomotor delay, behavioral clutter, and concomitant upper extremity deformations.[1] W. Brachmann reported the primary case of Cornelia de Lange disorder (CdLS) in 1916, taken after by Cornelia de Lange, a Dutch pediatrician, in 1933, after whom the clutter was named.[2] Other equivalent words incorporate Brachmann-de Lange disorder (BdLS), de Lange disorder, and Cornelia de Lange disorder range.[3] An evaluated 1:10,000 to 1:30,000 live new-borns are influenced by the overwhelming multisystemic mutation disorder known as Cornelia de Lange disorder (CdLS).[4] Experienced pediatricians and clinical geneticists can distinguish classic (or normal) CdLS from birth due to characteristic craniofacial see and developmental patterns, as well as limb deformities. In any case, not each individual with CdLS has the ordinary phenotype and can be displayed in an assortment of ways, extending from mellow to extreme and with shifting levels of facial and limb association.[5]

Aberrant gene expression is thought to be the underlying mechanism of CdLS.[6,7] Strong facial features, growth limitation, hypertrichosis, and upper-limb reduction abnormalities are characteristics of severe (classic) CdLS. Synophrys, thick or highly arched eyebrows, long eyelashes, anteverted nares, a short nasal bridge, widely spaced teeth, and microcephaly are cranial characteristics. A person's Intelligence Quotient (IQ) can range from 30 to 102 and many are autistic and self-destructive. Cardiovascular septal abnormalities, myopia, hearing loss, gastrointestinal issues, and hypoplastic genitalia or cryptorchidism are other prevalent occurrences. The diagnosis of CdLS is made with a proband with clinical features and/or by molecular genetic testing that recognizes a Nipped-B - like protein (NIPBL), RAD21, chromosome pattern maintenance protein 3 (SMC3), or a hemizygous pathogenic variant. Bromodomain-containing protein 4 (BRD4) or histone deacetylase 8 (HDAC8) or chromosome structure maintenance protein 1A (SMC1A).[8] Specific supportive and symptomatic therapies are used to treat CdLS.

AETIOLOGY

Although some families exhibit autosomal dominance, most incidences are sporadic. In 50% to 60% of cases, the culprit is a mutation in the NIPBL gene, which encodes part of the cohesion complex on chromosome 5p13. SMC1A, SMC3, RAD21, and HDAC8 are other genes identified to cause X-linked or mild forms of Cornelia de Lange syndrome.[9]

The HDAC8 and SMC1A genes are located on a sex chromosome, specifically the X chromosome. The condition is caused by only one copy of the defective gene and affects both boys and girls. This is in contrast to many other X-linked illnesses, where men are disproportionately affected. The autosomes, or non-sex chromosomes, include the NIPBL, RAD21, and SMC3 genes,

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and just one copy of the mutant genes are required to induce the illness. The five CdLS-associated genes synthesize proteins that are important in prenatal development. Particularly, the proteins are in charge of directing the growth of the face, limbs, and other body parts.[10]

CLINICAL FEATURES

Patients with CdLS may exhibit growth restriction while still in the womb. They frequently weigh less than 2.2 kg at birth and exhibit failure to thrive. The children frequently continue to experience delayed growth as they get older. Although classic (or typical) CdLS is easy to recognize, rare changes can complicate the diagnosis.[11]

Of the various organ systems and phenotypical manifestations that may exist.

Craniofacial: CdLS patients may also have micrognathia, choanal atresia, cleft palate, small upturned nose, thin vermilion margin or philtrum, or excessive teeth.[12] Children with CdLS often have thick, centrally gathered eyebrows on their faces.[13] Long eyelashes, droopy ears, External Auditory Canal (EAC) abnormalities, external auditory canal atresia, brachycephaly (short bones), and microcephaly (small bones) are other important factors. In addition to hirsutism, children may have hairs on the forehead and neck area.

Neurodevelopmental: Children can suffer from global developmental delays as well as intellectual disabilities.[11]

Gastrointestinal: Eighty-five percent of patients with CdLS have GERD, which puts them at risk for developing Barrett's esophagus.[12] Other signs consist of nausea, vomiting, diarrhea, constipation, trouble feeding, or a lack of appetite. Pyloric stenosis, gastrointestinal rotation, and diaphragmatic hernias are more specific gastrointestinal anomalies.[11]

Genitourinary: Common conditions include genital hypoplasia, renal hypoplasia, hypospadias, and cryptorchidism (73% of males have this condition). Males with CdLS have been reported to have Benign Prostatic Hypertrophy (BPH).[12]

Ophthalmology: Children with CdLS frequently present with lacrimal duct dysfunction, strabismus, ptosis, nystagmus, astigmatism, myopia, amblyopia, cataract, glaucoma, retinal detachment, and blepharitis.[1] Overall, 50% of people have some sort of visual impairment.

Cardiovascular system: Murmurs, aortic coarctation, pulmonary stenosis, tetralogy of Fallot, and atrial or interventricular septal abnormalities are some of the cardiac symptoms in children with CdLS.[11]

Musculoskeletal system: Patients with CdLS show limb dysplasias, scoliosis (39%), partial toe fusion, clinodactyly (curved fifth finger), radial hypoplasia, radioulnar synostosis, a truncated sternum, and pectus excavatum.[12]

Psychiatry: Patients may exhibit aggressive, self-destructive, or self-stimulatory conduct, among other behavioral issues. Obsessive-Compulsive Disorder (OCD), depression, attention deficit hyperactivity disorder (ADHD), and anxiety are frequently co-occurring disorders with CdLS.[12]

Neurology: Up to 25% of patients have seizure disorders that need neurologist care. There have also been reports of autonomic dysfunctions and issues with sleep, such as nocturnal apnea and insomnia.[13]

Dermatology: May indicate hirsutism or hypertrichosis or cutis marmorata (bluish-red marbling patterned skin).[13]

Respiratory: Laryngeal abnormalities are uncommon.

Immunodeficiency: Ear infection (53%), viral respiratory tract infection (46%), pneumonia (42%), sinus infection (33%), oral candidiasis (13%), sepsis (6%), and skin infection (4%) and the most frequently reported disease recurrence in CdLS patients.[14]

DIAGNOSIS

Clinical features suggest CdLS as the primary diagnosis. Mutations in the five CdLS genes can be used to diagnose atypical patients and confirm the diagnosis in individuals with normal characteristics. When genetically tested the NIPBL mutation is responsible for 80% (70% of those tested) of CdLS patients. Although this is a very large gene with 46 coding exons (long isoforms), the first step in genetic testing is to screen NIPBL for disease-causing mutations using Sanger sequencing, again starting with the evolution of hotspots.[4]

When no NIPBL mutations are detected, several genes will be searched, starting with SMC1A (25 coding exons) analysis, followed by HDAC8 (11 coding exons), RAD21 (13 coding exons), and SMC3 (29 coding exons) analysis. However, approximately 30% of patients do not have a disease associated with this gene mutation; therefore, search using next-generation large-scale sequencing (NGS) or whole-exome sequencing of the genome containing all known cohesin pathway genes (WES). With increasing coverage of exome sequences and decreasing costs, this method will become the standard test in the future.[15]

Somatic mosaicism has recently been reported for NIPBL, SMC1A, and SMC3.[16,17] Changes cannot be observed in blood lymphocytes, but have been found in patients' mouth cells or saliva. Somatic mosaicism of SMC1A and SMC3 was found in one case, while NIPBL was more common. For individuals who do not detect NIPBL mutations in their blood DNA, other tissues can be explored.[17] Diagnosis of CdLS is simple because of its appearance, but overlapping features and chromosomal abnormalities must be considered.

TREATMENT

Lifetime Treatment, Collaboration, and Relationships are essential for diagnosing CdLS. Health care and quality of life can be improved through diagnosis, counseling, and assessment by a multidisciplinary team. However, barriers to receiving care may include physical or behavioral problems, isolation from others, and financial concerns. People with CdLS are more likely than people without CdLS to experience delayed treatment, hospitalization, more serious complications, and longer hospital stays. Regular health checks, planning for entry and exit, and the use of manual custom procedures are important aspects of treatment.[18,19]

Facial and cranial features common in CdLS include low ears, retracted jawbone, straight and long philtrum, thin lips, and short, upturned, and anteverted nostrils. Differentiation of the appearance of CdLS is readily accessible by 2D and 3D ultrasonography in the early second trimester.[20]

Checking for genital abnormalities, performing prompt diagnostic procedures, and providing adequate treatment are necessary for female CdLS patients, particularly those with Vesicoureteral Reflux (VUR). Doing so will help prevent urinary symptoms, lessen resistance during voiding, reduce the likelihood of secondary VUR, and manage recurrent UTIs.[21]

CdLS can result in endocrine system dysregulation, especially in people at risk for insulin resistance who have high HOMA-IR values and insulinemia. For those with CdLS, clinical follow-ups, including hormonal evaluations, are recommended.[21]

Speckle analysis can detect early cardiomyopathy in CdLS patients before symptoms and changes in other echocardiographic or analytical parameters. For all the above reasons, cardiovascular therapy is recommended, especially in the young, even in the absence of CHD.[22] Because 25% of CdLS patients have heart disease and 10% have renal failure, all infants and children should have a regular renal ultrasound and echocardiography performed.[23]

Almost all infants and toddlers with CdLS experience feeding problems commonly experienced by both children and adults. Oral feeding is better if the daily feeding time does not exceed 3 hours. It is safe and stress-free; otherwise, breastfeeding is recommended.[24]

A minor delay in puberty in diagnosed patients (mean age of onset 15 in boys and 13 in girls). A bicornuate uterus is found in 19% of women, and approximately 80% of women develop breast tissue. 80% of men with CdLS have cryptorchidism, 37% have small testicles, and 9% have hypospadias.[25]

Hypertension and congestive heart failure were reported in 4-8% and 2-4%, respectively, of CdLS patients.[12] There is a report of fatal coronary occlusion with pulmonary embolism.[26]

Creatinine clearance abnormalities occurred in 24% of patients, out of 30% of adults with kidney abnormalities. Monitoring of renal function is recommended when an individual has renal failure.[27]

By the age of 41 years, 10% of males had enlarged prostates, which in one case necessitated prostate resection.[28] Recommendations should be followed when screening for breast and cervical cancer.[29] Gastroesophageal Reflux Disease (GERD) is the most severe and severe gastroesophageal reflux disease in childhood that can present with clinically significant Sandifer-like dystonia. GERD can manifest in a variety of ways, including poor diet, recurrent (toxic) pneumonia, growth retardation, weakness, fatigue, or poor sleep.[30,31] In a cross-sectional study, individuals with the NIPBL variant had a 71% higher incidence of GERD than those with the SMC1A variant (60%).[32] Numerous individuals who have had GERD for a long time have acquired esophageal adenocarcinoma as young adults.[33,34] Our combined experience shows that people with CdLS and GERD respond well to high doses of proton pump inhibitors (omeprazole 0.735 mg/kg per day; half of the dose is usually required for maintenance), similar to those with neurological deficits.[35,27] Since chronic GERD is frequently a contributing factor to the development of Barrett's esophagus, long-term follow-up is advised.[36]

Especially if the chin supports the jaw (present in 57% of patients), this can cause weakness or amblyopia (also known as thief's eye) or refractive error thought to be associated with ptosis. The treatment for blepharitis is the same as for the general population: Wash the eyelids with baby shampoo or specialized scrubs. Surgical exploration and drainage of nasolacrimal duct obstruction should be sought only if symptoms of putative blepharitis do not improve after treatment. Intubation of the nasolacrimal duct and surgical treatment (dacryocystorhinostomy) may be necessary for severe occlusion.[37,38] Surgical refractive therapies could enhance vision.[39] One-third of CdLS patients have a narrow ear canal, low, hairy, and abnormal ears.[40] The middle ear and inner ear abnormalities in patients with CdLS include malformed vestibule, cochlear abnormalities, tiny mastoids, and soft tissue opacities in the tympanomastoid space. There are different treatments depending on the type and severity of hearing loss. For example, myringotomy and the insertion of pneumatic ear tubes are the first-line treatments for, mastoidectomy and chronic or recurrent otitis media with effusion may be an option if soft tissue is filling the mastoid and the middle ear.[41,42]

Those with SMC1A mutations have a 45% seizure prevalence, those with NIPBL variants have 15%, and those without molecular evidence have 20–26%.[43] CdLS patients exhibit intellectual impairment. Environmental enrichment tactics should be a part of management techniques to promote cognitive and educational abilities.[44]

PROGNOSIS

Adults with Cornelia de Lange syndrome have only very rarely been recorded as having the condition. Life expectancy is mostly unchanged; however, if the patients experience any problems from the illness, their prognosis will largely depend on the degree and treatment of those complications.[14]

COMPLICATIONS

Many organ systems are affected by CdLS; therefore, complications may occur that need therapy from a particular specialization, such as:

Gastroenterology: Early infancy may call for the treatment of congenital diaphragmatic hernia, malrotation, or pyloric stenosis.[26] Barrett's esophagus or aspiration pneumonia may be made worse in children with GERD (in 10% of cases).[45]

Urology: Cryptorchidism or hypospadias is common in boys with CdLS amid the earliest stages. Orchiopexy is recommended for the treatment of cryptorchidism because of the potential for testicular cancer.[46] Genital hypoplasia affects both sexes equally.[14]

Nephrology: Children with CdLS frequently experience renal cysts and renal hypoplasia.[14]

Young patients with CdLS have shown early aging symptoms such as osteoporosis or canities (premature hair thinning). The genetic defect in the cohesin pathway, which prevents cell mitosis, may be the cause of premature aging in CdLS.[25]

CONCLUSION

CdLS is a rare condition characterized by facial and limb abnormalities, strong facial features, and growth limitations. It is diagnosed through clinical features or molecular genetic testing. Treatment involves supportive and symptomatic therapies. CdLS patients face delayed treatment, hospitalization, complications, and longer stays. Regular health checks, planning, and customs procedures are crucial. Female patients should check for genital abnormalities, perform diagnostic procedures, and provide adequate treatment. Early cardiomyopathy detection is essential. Long-term follow-up is advised.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

CdLS: Cornelia de Lange disorder; **IQ:** Intelligence Quotient; **NIPBL Nipped-B:** like protein; **RAD21:** RAD21 cohesin complex component; **SMC3:** Chromosome pattern maintenance protein 3; **BRD4:** Bromodomain-containing protein 4; **HDAC8:** Histone deacetylase 8; **SMC1A:** Chromosome structure maintenance protein 1A; **EAC:** External Auditory Canal; **GERD:** Gastroesophageal reflux disease; **BPH:** Benign Prostatic Hypertrophy; **OCD:** Obsessive-Compulsive Disorder; **ADHD:** Attention Deficit Hyperactivity Disorder; **NGS:** Next-generation large-scale sequencing; **WES:** Whole-exome sequencing; **VUR:** vesicoureteral reflux; **HOMA-IR:** Homeostatic model assessment of insulin resistance; **CHD:** Congenital heart disease.

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