Cornelia De Lange Syndrome and Orofacial Implications

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Abstract

Background and objective: Cornelia de Lange syndrome is a rare disease with a very wide and genetically heterogeneous phenotypic variability that affects multiple organs and systems. This work consists of a narrative review on Cornelia de Lange syndrome, specifically addressing its orofacial manifestations and the impact of these changes on dentistry.

Methods: For the bibliographic search, the following databases were used: PubMed Central (PMC), Online Knowledge Library (B-ON), Cochrane Library and Scientific Electronic Library Online (SciELO), as well as Google Scholar. The keywords used in English and Portuguese, were Cornelia de Lange syndrome, Brachmann de Lange, dental manifestations.

Results: So far, pathogenic mutations have been identified in five genes: *NIPBL, SMC1A, SMC3, RAD21* and *HDAC8.* The diagnosis of most children is usually obvious at birth. Brachycephaly and synophry are characteristics present in all children with Cornelia de Lange syndrome, being also common the presence of mental retardation. Frequent manifestations include excess facial hair and generalized hirsutism, unusually long curly upper and lower eyelashes. Small, spaced teeth with delayed eruption, partial anodontia, thin upper lip, depressed corners of the mouth, and occasionally arched or cleft palate may also be present.

Conclusion: The multidisciplinary strategy is the key to treatment success. It is important to provide the family with information about the syndrome, which can help parents to cope emotionally with the situation and cooperate in the treatment of their child.

Keywords: Cornelia de Lange Syndrome; Brachmann de Lange; Dental Manifestations

Introduction

The Cornelia de Lange syndrome (CdLS), also called Brachmann de Lange syndrome is a rare, genetically heterogeneous disease that affects multiple organs and systems. The first cases were reported by the Dutch anatomists Gerardus and Willem Vrolik in 1849, by a German doctor Brachmann in 1916, followed by the Dutch pediatrician Cornelia de Lange in 1933, responsible for the name of this pathology [1-3]. In recent decades, several genetic causes of CdLS have been identified, such as mutations in five genes encoding structural components of the cohesion complex (the proteins NIPBL, SMC1A, SMC3, RAD21 and HDAC8) [4]. CdLS is a clinically variable disorder characterized by psychomotor delay and intellectual disability, distinct facial features, delayed pre- and postnatal growth, hirsutism and upper limb malformations [5]. The craniofacial characteristics of this syndrome include microbraquicefalia, sinophris, arched eyebrows, depressed nasal bridge, anteverted nostrils, long filter, thin upper lip, high arched palate, late tooth eruption, small and spaced teeth, micrognathia, among others [6]. CdLS patients need multidisciplinary follow-up from birth. These patients are not cooperative due to their mental disability and low motor mobility. Therefore, early intervention for the prevention of associated pathologies and adaptation to the dental office is of great importance. All of this shows how important it is to know CdLS and its facial and oral characteristics in order to obtain a correct diagnosis and apply an appropriate approach treatment. The present study aims to describe the most common general and orofacial manifestations observed in patients with CdLS as well as the therapeutic approach during dental consultation.

Methods

This work consists of a narrative review about CdLS, specifically addressing its orofacial manifestations and the impact of these changes on dentistry. For the bibliographic search, the following databases were used: PubMed Central (PMC), Online Knowledge Library (B-ON), Cochrane Library and Scientific Electronic Library Online (SciELO), as well as Google Scholar. The keywords used in English and Portuguese, were Cornelia de Lange syndrome, Brachmann de Lange, dental manifestations. Priority was given to papers published between 2009 and 2019. Papers published before this period was also used if considered relevant for the work. This search led to the selection of a total of 82 bibliographic references.

Etiology

CdLS is a rare multisystemic disease, sporadic in most cases. However, some families demonstrate an autosomal pattern of inheritance. It is mainly characterized by a distinct facial phenotype, anomalies in the upper limbs, as well as, growth and psychomotor retardation. Most signs and symptoms of CdLS can

be recognized at birth or even be detected by ultrasound imaging during pregnancy. The incidence is 1 case per 10,000 to 50,000 births, with no difference between races and genders reported so far. Most children do not survive over 2 years of age, being the main cause of death pneumonia associated with cardiac, respiratory and gastrointestinal abnormalities [7-9]. The CdLS shows not only clinical, but also genetic heterogeneity. So far, pathogenic mutations leading to CdLS, have been identified in five genes: *NIPBL, SMC1A, SMC3, RAD21* and *HDAC8* [10-13]. Mutations in the *NIPBL, SMC3* and *RAD21* genes lead to the autosomal dominant form of CdLS (AD-CdLS), while the genes causing CdLS linked to the X chromosome are *SMC1A* and *HDAC8*. Mutations in the *NIPBL gene* represent 80% of all cases of this pathology [14]. All mutations identified as responsible for the development of CdLS, affect proteins/enzymes in a single metabolic pathway, the cohesin pathway. Thus, together with Roberts syndrome and Warsaw Breakage syndrome, CdLS belongs to a group of diseases called cohesinopathies [15-17]. The cohesin complex is involved in chromosomal segregation, DNA repair and regulation of the expression of certain genes. However, CdLS is thought to arise mainly through transcriptional deregulation [15-17]. The protein products of three of the identified genes (*SMC1A, SMC3* and *RAD21* genes) are structural components of the cohesin ring. The protein encoded by the *NIPBL* gene is involved in the loading of the chromatid in the ring during the metaphase while the product of the *HDAC8* gene is responsible for the deacetylation of the *SMC3* gene in order to facilitate the reorganization of the cohesin complex after its dissociation from the chromatin during prophase or anaphase [15-17]. The cohesion ring, capable of involving the DNA strands, is composed of four main subunits, *SMC1, SMC3, RAD21* and STAG1/2. There are several other proteins involved in loading (NIPBL, MAU2), establishment (HDAC8, ESCO2) and release (WAPL, PDS5B) of the ring. Mutations in the genes *NIPBL, SMC3, SMC1A, RAD21* and *HDAC8* are associated with the development of CdLS, while the ESCO2 defect is associated with Roberts syndrome [18].

NIPBL gene

The *NIPBL* gene, located on chromosome 5 (p13.2) is ubiquitously expressed, including the tissues/organs affected in CdLS. This gene has a higher expression in the heart and skeletal muscles [7,10,19].

A wide spectrum of chromosomal changes and single nucleotide changes have already been identified in the *NIPBL gene*. To date, 333 different mutations in this gene have been identified in heterozygotic condition in 391 patients with CdLS [20-22]. Two independent groups identified a balanced chromosomal translocation between chromosomes 5 and 13 (t (5.13) (p13.1; q12.1)) in the same patient with CdLS [7,10] and, subsequently, several types of mutations in the *NIPBL* gene, including mutations at the splice sites, as well as missense, nonsense and frameshift mutations were identified in patients with CdLS [10,23-26]. Most of these changes lead to premature arrest of protein synthesis, leading to the production of a partially functional or non-functional truncated protein [20].

SMC1A gene

Mutations in the *SMC1A* gene (Xp11.22) are responsible for 5% of clinically diagnosed CdLS cases [11]. So far, 36 different mutations (28 missense mutations, 1 splice site mutation and 7 in-frame deletions) have been identified [11,20,27-29]. In addition, a translocation (t (X, 8) (p.11.2; q24.3)) and an intragenic deletion of approximately 8 kb (exons 14-16) have been reported [30,31]. The *SMC1A* gene partially escapes the inactivation of the X chromosome and mutations have been identified in both sexes with a female:male ratio of 2.4:1 [32]. Failure to identify mutations that lead to premature arrest of SMC1A production may imply that they are not tolerated or perhaps lead to a different phenotype [33].

HDAC8 gene

The *HDAC8* gene is located on the X chromosome (q13.1), being submitted to X inactivation [12]. So far six different mutations in this gene (five missense and one nonsense) have been identified in patients with CdLS [12,34]. Moreover, 22 different mutations (11 missense, two nonsense, one splice site and eight intragenic insertions/deletions) have been described in patients with CdLS characteristics, such as ocular hypertelorism and large fontanelles [14]. All identified missense mutations lead to reduced enzyme activity or total absence of the enzyme [12,14,34]. The complete loss of the HDAC8 protein function seems viable in humans, since some missense mutations result in decreased enzyme activity. This is further reinforced by the discovery of a man with a partial deletion of the *HDAC8* gene and another with undetectable levels of HDAC8 protein [12,14]. A single truncating mutation of the HDAC8 protein has been identified in a Dutch family with symptoms like the Wilson-Turner syndrome [35].

RAD21 and *SMC3* genes

Mutations in the genes *RAD21* (8q24.11) and *SMC3* (10q25.2) have only been described in a few patients. The four intragenic mutations in the *RAD21* gene identified so far are: two missense mutations, a base pair duplication and an in-frame deletion of exon 13 inherited from a slightly affected mother. A splicing site mutation (c.274 + 1G>A) inherited from an apparently unaffected parent has also been reported. In addition, four patients with characteristics consistent with changes in the cohesin pathway were shown to have a microdeletion on chromosome 8 (q24.1), where the *RAD21* gene is present [13,29,36]. The first identified mutation in the *SMC3* gene was a 3 bp deletion in a male patient with mild symptoms [11,17]. Since then, Ansari et al. [29] identified five additional patients with mutations in this gene (two missense, two small intragenic deletions and one nonsense mutation).

Somatic mosaicism in Cornelia de Lange syndrome

Approximately 65% of individuals with a clinical diagnosis of CdLS have a positive blood test for one of the five discussed genes. This leaves 35% of individuals with a confirmed diagnosis, but without a defined molecular etiology. The existence of such

a large percentage of individuals without a genetic explanation, leads to suspect that there are additional mechanisms involved in the development of CdLS yet to be discovered [37].

Somatic mosaicism of the *NIPBL* gene was reported in a small number of individuals [37]. Somatic mosaicism was also identified in the *SMC1A* and *SMC3* genes [38]. Mosaicism occurs when an individual contains two or more genetically distinct cell lines. Generally, these mosaic mutations are not detected by standard tests on DNA isolated from blood. Therefore, the diagnosis requires the analysis of a different type of tissue, in addition to blood, in order to rule out the presence of a mutation in other tissues [29]. Somatic mosaicism was found in one of the patients with a small deletion. The patient's phenotypic characteristics included severe microcephaly and atypical facial appearance [29].

The role of placenta in the etiology of Cornelia de Lange syndrome

Guinea pig studies have shown that mutations involved in the development of CdLS can compromise several aspects of embryonic development, including the formation of bones, limbs, heart and intestine. A very common feature associated with CdLS is slow growth and small size. Some studies have indicated that a protein produced by the placenta (PAPP-A) was often low during pregnancy [39,40]. As the size of the placenta is generally proportional to the size of the embryo, a smaller placenta, with a deficient production of PAPP-A, explains the development of smaller embryos, as happens in CdLS. However, a second possibility is that the placenta itself is dysfunctional due to the triggering CdLS mutation, regardless of the size of the placenta/embryo. Recent work has revealed the high prevalence of placental defects and their contribution to the abnormal development of embryos in guinea pigs [41]. These researchers studied whether placental dysfunction can contribute to embryonic development phenotypes associated with CdLS models in guinea pigs and found that the size and development of the placenta are negatively affected by the loss of HDAC8 and NIPBL proteins, regardless of the effect of these proteins on embryonic development [41].

Signs and Symptoms

This is a multisystemic malformation syndrome, with a very wide phenotypic variation. The diagnosis of most children is usually obvious at birth, but due to the wide clinical phenotypic variation, several milder forms of this syndrome are not generally recognized. The most frequent features involve the hands and face. Severely affected children are unable to thrive and demonstrate significant mental commitment. Common initial problems include feeding difficulties, convulsions, irritability, a deep hoarse scream and obvious anomalies in the limbs [9].

General manifestations

Changes in the upper limbs

Ulnar dysplasia is the most common upper limb phenotype in CdLS. This anomaly can range from partial to complete absence of the ulna, radial dysplasia and humerorradialsynostosis [9].

The most characteristic sign is ulnar and radial hypoplasia on both sides. The hand may contain a few fingers or more than five. Ectrodactyly is common with ulnar fingers more absent than radial fingers. A biphalangeal thumb on the radial side of the hand is the single most persistent finger on a monodactyl hand. Many of the two-fingered hands are unstable at the Carpometacarpal level, like a typical slit hand with a very deep central slit. Many hands with two or three fingers, referred to in the literature as oligodactyly, have a soft tissue membrane connecting these fingers. Many of the thumbs lack tenar musculature and a normal space, being referred to in the literature as "proximal implant thumbs". Kirner deformations of the fifth finger and a simian palm fold can also be observed [42,43]. Clinodactyly of the fifth finger is present in 88% of these children. Skeletal maturation is delayed. The carpal coalition may involve distal and proximal ranks [44]. Focomelia and antecubitalpterygium, an unpleasant condition like "chicken wing-like appendages" (displacement of the radial head with secondary contraction of the elbow) with ulnar deviation, may be present. The elbow flexion contracture is typically inflexible. In addition, the movement of the glenohumeral joint is generally limited. These contractures are present at birth and persist if they are not subjected to surgery. The contralateral limb may be normal, but it is usually affected [9]. The lower limbs are less affected. Typical findings are small feet and partial syndactyly of the 2nd and 3rd toes [5]. Orthopedic complications include hip dysplasia/dislocation, scoliosis, rigid Achilles tendons and the development of bunions. Scoliosis, cervical malformations and pectus excavatum are also associated with CdLS [5,42,45]. The onset of osteoporosis may be earlier than expected [46].

Neurological and sensorial changes

Hearing loss is observed in most patients with CdLS, including sensorineural diseases and conductive hearing loss. The ear canals are often narrow or stenotic, which predisposes patients to otitis media and sinusitis [47].

The most common ophthalmic findings are high myopia, ptosis and blepharitis. Nasolacrimal duct obstruction, nystagmus, cataracts and glaucoma have also been reported [5]. Epilepsy is found in 20% of patients, with partial epilepsy being the most common type [48]. These patients usually have an abnormally high tolerance to pain, which in some cases can be caused by neuropathy. If they can walk, the gait is usually wide, with a slight curved position [46].

Gastrointestinal manifestations

Gastroesophageal Reflux Disease (GERD) is present in more than 90% of patients. Individuals with CdLS and GERD usually have "atypical signs" such as hyperactivity, vomiting and night agitation. The incidence of GERD is not significantly different in patients with classical vs mild CdLS. However, there is a strong correlation between the degree of esophageal damage and the clinical phenotype [49]. GERD usually persists or worsens and there may be long-term sequelae, including Barrett's esophagus, which appears in 10% of cases [38]. Feeding problems are frequent and are generally seen in childhood and young adults, and can be caused by cleft palate, micrognathia, decreased

muscle tone in the oral area or by GERD. Aspiration pneumonia is a frequent complication [5]. Pyloric stenosis, observed in 4% of patients, is the most frequent cause of persistent vomiting in the neonatal period. Other gastroesophageal abnormalities include poor intestinal rotation (2%) and congenital diaphragmatic hernia (1%) [38].

Cardiovascular manifestations

The incidence of congenital heart disease in patients with CdLS is about 25 to 30%. The most common cardiovascular changes include, in decreasing order of prevalence, ventricular septal defects, atrial septal defect, pulmonary stenosis, tetralogy of Fallot and hypoplastic left heart syndrome [5,50].

Genito-urinary manifestations

Up to 40% of patients with CdLS have structural abnormalities in the kidneys and/or urinary tract, such as vesico-ureteral reflux, pelvic dilation and renal dysplasia. Renal function may be reduced. Hypoplastic genitalia and cryptorchidism are reported in 57% and 73% of male patients, respectively. Other common findings are micropenis and hypospadias [5]. Smaller labia majora and an abnormality in the formation of the uterus can be observed, and fertility may be decreased in severely affected women[5]. However, maternal and paternal transmission of this syndrome has been reported, with even several cases of mildly affected parents with severely affected children [31,36,51,52].

Skin manifestations

Generalized hirsutism, more visible on the face, back and extremities, is frequent, with 60% of individuals presenting cutis marmorata. Small nipples and navels can also be seen [5]. Patients show signs of premature aging, such as wrinkles, flabbiness and grey hair, looking older than chronological age [46].

Paraclinic findings

Transient and/or immune thrombocytopenias were observed in CdLS, with the impaired T-cell population associated with antibody deficiency [53,54].

Oral and craniofacial manifestations

Facial features in CdLS are distinct and diagnosis is usually made easily. Brachycephaly and sinophris are characteristics present in all children with CdLS. Frequent manifestations are also excessive facial hair and generalized hirsutism, curly and unusually long upper and lower eyelashes, and low anterior and posterior hairline. Microcephaly, small and widely spaced teeth, with delayed eruption, partial anodontia, thin upper lip, depressed corners of the mouth and occasionally arched or fissured palate may also be present. These patients have a crooked nose, depressed nasal bridge, long filter, low ears and short neck [6,55,56].

Individuals with CdLS can also present dental malocclusions of class II or III, open bite or crossbite due to the bad development of the jaws [6].

Classification, Diagnosis and Prognosis

Van Allen et al. [57] proposed a CdLS classification system according to the intensity of the phenotype. Patients with "classic" or type 1 CdLS have facial and skeletal changes. Patients with the "mild" form of this syndrome or type 2 have less intense facial and skeletal changes, like those seen in type 1. However, these changes may develop later or may be only partially expressed. The "phenocopy" or type 3 CdLS includes patients who have phenotypic manifestations, which are randomly related to chromosomal aneuploidies or teratogenic exposures [57]. The patient's history provides clues relevant to the diagnosis, such as the course of pregnancy and child birth. Premature delivery is seen in 30% of CdLS cases. The initial diagnosis can be made by ultrasound between 20 and 25 weeks of gestation. The most obvious anomaly seen is the absence of an upper limb or the presence of an abnormally short upper limb. The 3D ultrasound examination reveals long eyelashes, hypertrichosis, low ears and micrognathia, and the presence of a small jaw will interfere with the newborn's feeding [58]. The diagnostic criteria for CdLS were formulated by the CdLS Foundation. Therefore, clinical findings must meet facial criteria, as well as criteria for two to three of six other categories of systems. It is necessary that at least one of the systems involved is in one of the following areas: growth, development or behavior [18]. As the facial features of patients with CdLS become less typical, photographs of the patient from childhood can be useful in their assessment [59]. In order to establish the diagnosis in atypical suspected cases and confirm the diagnosis of patients with classic characteristics, analysis of mutations in the 5 known genes involved in the development of CdLS can be performed. Among patients with CdLS, where a genetic mutation has been identified (representing 70% of the investigated patients), mutations in the *NIPBL* gene are responsible for 80% of cases. Therefore, the first step in genetic testing is to track the *NIPBL* gene, in critical mutation regions, since it is a relatively large gene with 46 exons [20]. When a mutation in the *NIPBL* gene is not identified, other genes are investigated, starting with the analysis of the *SMC1A* gene (25 exons), followed by the *HDAC8* gene (11 exons), *RAD21* gene (13 exons) and, finally, the *SMC3* gene (29 exons). However, about 30% of patients do not have mutations in these genes. In these cases, next generation sequencing analysis with a genetic panel that includes all known genes encoding enzymes in the cohesin pathway or even the total exome sequencing can be considered [18]. The diagnosis of the classic form of CdLS is quite simple due to the typical facial features. However, CdLS may have phenotypic characteristics common to other syndromes, such as Siris coffin syndrome, Fryns syndrome, partial duplication of the long arm of chromosome 3 (3q), fetal alcohol syndrome, Rubinstein-Taybi, Roberts syndrome, Warsaw rupture syndrome and KBG syndrome, among others [18]. Most children with CdLS have intellectual disabilities, often needing supervision throughout life and at work when they reach adulthood. Life expectancy depends on the number and severity of complications present, but it is estimated to be 10 to 20 years shorter compared to the general population [60,61]. The most common causes of death are respiratory diseases, including aspiration/reflux,

gastrointestinal diseases such as obstruction and volvulus, congenital abnormalities such as diaphragmatic hernia and heart disease and seizures [62].

Social and Psychological Impact

The inclusion of CdLS patients in society is difficult, not only because they have particular phenotypic characteristics, but also due to behavioral problems. Several behavioral changes have been associated with CdLS, including aggression, hyperactivity, autism and injury from operational stress [63]. A prevalence of self-harm in CdLS patients was estimated between 16.6 and 63.6% [64], although no control group was used. The most described forms of self-harm were biting oneself and attacking one's head and body. It has been suggested that self-harm is biologically determined by an abnormal neuroanatomy, leading, in part, to the behavioral phenotype of CdLS [65].

However, biological factors may not be the only cause of self-harm in patients with CdLS, having been reported by Moss et al. [66] that in some of these patients, this self-aggression is associated with environmental stimuli, such as hospital change. This characteristic is also observed in many patients with inadequate cognitive communication skills. This cognitive deficit can vary from mild to severe, and there may even be a comorbid diagnosis (associated with other syndromes), including social anxiety, selective mutism, intellectual disability, hearing loss and motor speech disorders [67].

Brylewski [68] reported that most of these patients have an IQ below 50, being within the range of mild to moderate mental retardation, evidenced by joint errors, with sound substitutions and distorted or absent consonants. In this study, only 15 patients had an IQ equal to or greater than 50, and of these, only five were 2 years old or less. Furthermore, only two patients with CdLS had intelligence within normal limits [68].

Treatment

Children with CdLS generally have a wide variety of health problems, making it important for all specialists to be aware of the child's special needs. The multidisciplinary strategy is the key to the successful treatment of children with syndromes, and should include a dentist, cardiologist, gastroenterologist, endocrinologist, urologist, psychologist and specialist in otorhinolaryngology. Family support is also essential, especially at the time of diagnosis. It is important to provide the family with information about the syndrome, which can help parents to deal with the situation emotionally and cooperate in the child's treatment [69].

One of the biggest problems in these patients is the possible difficulty in feeding due to transient dysphagia since birth. Studies show that, in the first stage, the nasogastric tube is the most used in nutritional support, being generally the most appropriate route in patients who need enteral feeding in the short term. Over time, most patients with CdLS achieve normal oral nutrition. Naturally, the more severe the clinical situation (the presence of large malformations in the upper limbs), the greater the likelihood of nutritional problems requiring support through a device such as the percutaneous endoscopic gastrostome [70]. This can be an indicator of a worse intellectual prognosis [70].

Treatment of oral cavity manifestations

At birth, it is very important to perform a complete physical examination in order to look for craniofacial anomalies associated with this syndrome. The presence of a cleft palate should be checked to plan correction before speech development. Due to the multisystemic involvement of this syndrome, including congenital heart defects, it is important to consult the patient's primary care physician before any procedure involving or not conscious sedation [71]. Most patients with CdLS need general anesthesia for treatment. The management of the airways and the application of the anestheticis challenging and must be specific for each patient. Certain complications can arise, such as cardiac arrest and difficult intubation, which are found more frequently inpediatric patients [72]. Further research focusing on airway clearance techniques and the application of specific anesthetics for this syndrome is needed to improve care. Thus, it is essential to develop specific techniques related to problems of intubation, oxygenation, ventilation and reduced risk of aspiration, in addition to other complications, for the success of treatment in all patients with CdLS [72].

The role of the pediatric dentist is to use strategies to control the patient's behavior and the preventive dentistry specialist should encourage the adoption of the use of fluorides, sealants, rigorous oral hygiene practices, providing timely dietary advice [73]. The treatment of specific dental problems such as gingival erosion and periodontal disease, as well as dental discrepancies, the extent of caries and the size of the jaw must be properly treated [74]. In addition, timely referral to a medical specialist, including the geneticist, cardiologist, gastroenterologist, endocrinologist, nephrologists, ophthalmologist, otolaryngologist and speech therapist should be done if necessary.

Finally, preventive monitoring from childhood and coordination with the pediatrician is necessary. Routine follow-up, every six months, facilitates the necessary changes in treatment resulting from changes in orofacial growth, the detection of pathologies and the maintenance of good oral hygiene at home [69].

Discussion and Conclusion

If anything catches the attention of CdLS, it is its great clinical and genetic heterogeneity. To date, five causal genes have been identified and it is not ruled out that in the coming years more genes might be found. According to the genotype-phenotype relations, a scale of clinical severity could be established, in which, in increasing order, the *SMC3* gene would be followed by *SMC1A*, *RAD21*, *HDAC8* and *NIPBL* genes. However, 80% of patients have a mutation in the *NIPBL* gene [14,20]. In a study of the Spanish population published in 2010, it had already been established that mutations in the *NIPBL* gene that produced a change in the DNA reading frame, were associated with a more serious phenotype [27]. New diagnostic strategies have reduced the number of undiagnosed patients, but there are still cases

without an established cause. In 2013, Huisman et al. reported that 23% of patients with a clinical diagnosis of CdLS had somatic mosaicism in the *NIPBL* gene and that the cells most suitable for diagnosis were those of the oral mucosa [37]. All of these developments served to modify the analysis protocol. Although peripheral blood leukocytes have still been used as the most common sample, due to negative results, the DNA of the cells of the oral mucosa should be studied [75].

Patients with this syndrome have skeletal defects in the upper limbs and craniofacial defects (brachycephaly, hypoplastic jaw, cleft palate, varying degrees of hirsutism, the eyebrows can be joined through the bridge of the nose (sinophris), in addition to hypertelorism and antimongoloid inclination of the eyes, upturned nostrils and thin lips [76-79]. Generally, patients with CdLS have some degree of mental retardation and therefore need to be treated as special children. The presence of caries, gingivitis, periodontal disease, supernumerary teeth, impacted teeth and crossbite is evident in these patients [6,74,80]. In addition, there may be cardiovascular, endocrine and gastrointestinal abnormalities [6,18]. Barret et al. [81] reported a case of CdLS, which presented problems in terms of tooth extraction and hemorrhagic diathesis that were thought to be due to a variant of von Willebrand's disease.The treatment in Dentistry is focused on the preservation of function and aesthetics. Endodontic treatment, when necessary to assist in restorative treatment, should be considered [80]. Fixed prosthetic treatment is more conservative than other considered alternatives, such as surgical correction of malocclusion. Other treatment methods that involve extractions of existing teeth and placement of removable dentures or extractions of these teeth combined with fixed or removable dentures supported by implants are considerably more radical and are more likely to have clinical complications than the conventional fixed and removable denture [82,83]. In conclusion, evaluations of patients with CdLS since childhood, by the dentist together with pediatricians and family members, facilitate the identification of changes in the orofacial growth, the detection of pathologies and the maintenance of oral hygiene, allowing care to be more focused on the needs of the patient.

Declarations

Authors have equally contributed to the elaboration of this paper. The authors have stated explicitly that there are no conflicts of interest in connection with this article. This article does not contain any studies with human participants or animals performed by any of the authors.

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