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CASE REPORT

Cornelia de Lange syndrome: a case report

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Abstract

Cornelia de Lange syndrome (CdLS) is a rare genetic disorder, caused by variants of cohesin complex genes. The disease is characterized by multiple congenital anomalies, which include distinctive facial features, prenatal and postnatal growth deficiency, neuropsychomotor delay, gastroesophageal reflux disease and upper limb malformations. We describe the case of a male patient who presented phenotypic alterations compatible with the classic form of CdLS. The diagnosis can be clinically determined even in the absence of molecular confirmation. Orogastric tube and admission to a neonatal Intensive Care Unit were necessary due to difficulties with suction. Subsequently, the patient underwent gastrostomy. In patients with CdLS, strict monitoring of weight gain, cardiac and urinary tract malformations and visual and hearing deficits is essential.

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INTRODUCTION

Cornelia de Lange syndrome (CdLS) is a rare disease characterized by multiple malformations, such as psychomotor growth retardation, cardiac, gastrointestinal, musculoskeletal and typical facies[1]. It results from mutations in genes that structure or regulate the cohesin complex, which, in turn, plays a role in chromatid cohesion, DNA repair and gene expression[2].

The prevalence ranges from 1:10,000 to 1:30,000 live births. Due to the heterogeneity in the phenotype, the disorder can present itself in different ways, which makes diagnosis difficult[3]. The etiology is still uncertain in many patients and the risk of recurrence is 2 to 5% for siblings of an affected individual[4].

The diagnosis, in addition to being based on clinical criteria, can be evidenced through the detection of abnormal copies and/or variation in the genotype sequence. In prenatal care, the diagnosis can be challenging, predicted from the combination of characteristics identified on ultrasound (USG), such as increased nuchal translucency, symmetrical intrauterine growth restriction (IUGR), limb and face anomalies.

This case report aims to correlate findings and procedures with data from the literature.

CASE REPORT

Newborn (NB) at term, born by cesarean section, with 37 weeks and 5 days of gestational age, Apgar 9/10, without need for neonatal resuscitation, weight 1,935 g (small for gestational age). Head circumference of 31 cm (microcephaly), abdominal circumference of 29 cm, chest circumference of 29 cm and length of 44 cm at birth.

A 23-year-old mother, G2PN1A0, had a history of gestational diabetes. Susceptible to toxoplasmosis; VDRL and HBsAg were non-reactive. Condylomata acuminata at 24 weeks of gestational age. Fetal malformations already presumed on ultrasound during prenatal care. Ultrasound performed at 12 weeks and 1 day of gestation showed nuchal translucency of 3.2 mm (reference value – RV: < 2.5 mm); Morphological USG at 24 weeks revealed mesomelia, acromelia, and bilateral oligodactyly; USG at 35 weeks and 5 days indicated fetal weight below the 3rd percentile (p3), with abdominal circumference also below p3. No infectious context during pregnancy and peripartum.

The following malformations were observed at birth: low-set ears, prominent forehead, retrognathia, acromegaly, bilateral oligodactyly, short upper limbs, ambiguous genitalia (absence of testes in the scrotum, micropenis), tuft of hair in the sacral region (Figures 1 and 2). From the phenotypic characteristics, with a detailed assessment of facial features and the help of a geneticist, the diagnostic hypothesis of CdLS was considered, confirmed by the clinical criteria recommended by the First International Consensus on the Diagnosis and Management of CdLS[3].

An echocardiogram showed an ostium secundum interatrial communication (IAC) measuring 1.42 mm, with a left-to-right shunt and an estimated Qp/Qs ratio of 1.06. His skull CT scan showed enlargement of the subarachnoid space in the middle fossa and sylvian fissures, septum pellucidum cavum, absence of signs of expansive processes and ventricular system with normal topography, morphology and dimensions. USG of the inguinal region showed the presence of testes. Kidney and urinary tract USG showed no changes.

Initially, the NB was sent to the regular infirmary. It was necessary to use an orogastric tube (OGT) for nutrition, due to difficulty in sucking. After administration of diet via OGT, the NB presented episodes of vomiting in large quantities, and was then referred to the neonatal ICU. He had a seizure, received phenobarbital (20 mg/kg via OGT), and had an episode of hyperthermia (39.1ºC). He was maintained in a regular dose of phenobarbital. For differential diagnosis with congenital adrenal hyperplasia, the following tests were ordered: 17-OH-progesterone: 1628 mcg/dL (RV: up to 22); total testosterone: 147 ng/dL (VR adults: 165-173); androstenedione: 6.1 ng/ml (RV < 1.6); basal cortisol: 9.5 mcg/dL (RV: 5.3-22.5); sodium: 134 mEq/dL; potassium: 6.7 mEq/dL.

He had a low water intake due to the OGT and oliguria. Initial attempts to obtain peripherally inserted central line (PICL) were unsuccessful. He received rehydration therapy via SOG, with improvement in diuresis. He evolved with tolerance to the diet via SOG, but did not progress in sucking/swallowing, requiring the performance of GTT. With good tolerance to the diet by GTT and adequate weight gain, he was discharged at 63 days of life for outpatient follow-up.

DISCUSSION

CdLS is a rare syndrome that affects growth, behavior and cognitive development, in addition to presenting systemic manifestations[3,5,6,7]. The classic type can be clinically recognized through the child's physical characteristics[3]. In the non-classical variant, the child may present more discrete characteristics[8]; this variant represents the majority of cases[9].

Prenatal diagnosis can be performed; however, it is rare. Ultrasonographic alterations can help in the diagnostic hypothesis, such as increased nuchal translucency, symmetrical IUGR, limb malformations and face anomalies[1,10,11,12,13]. Molecular studies can be performed by amniocentesis, aiding in the diagnosis. However, if no mutations are found, the diagnosis cannot be ruled out[1,3].

In the case reported, the following prenatal examinations showed:

1. USG at 12 weeks and 1 day GA: nuchal translucency = 3.2 mm;

2. Morphological USG with 24-week GA: mesomelia, acromelia and bilateral oligodactyly;

3. USG at 35 weeks and 5 days GA: fetal weight < p3, waist circumference < p3.

It is evident that the fetus had characteristics that could include CdLS in the main differential diagnoses. However, genetic testing was not ordered, given that the result would not interfere



Figure 1. Low implantation of the ears; long nasal filter; downward-sloping labial commissures; short upper limbs; bilateral oligodactyly.



Figure 2. Ambiguous genitalia; oligodactyly; hypertelorism in the sacral region.

with the conduct adopted later, a negative result would not rule out the hypothesis, and the cost would be high.

Postnatal diagnosis of children with malformations requires a thorough physical examination[14]. In CdLS, the diagnosis can be established through clinical criteria and/or by genetic screening with mutations suggestive of CdLS, involving the genes NIPBL, SMC1A, SMC3, RAD21, BRD4, HDAC8 and ANKRD11[3,8].

The First International Consensus on CdLS Diagnosis and Management in 2018 established the following diagnostic criteria[3]:

Cardinal signs (2 points)

1. Meeting of the eyebrows in the facial midline and/or thick eyebrows
2. Short nose, concave nose and/or anteverted nasal tip
3. Long upper lip and/or without furrow
4. Red upper lip and/or downward-facing labial commissure
5. Oligodactyly in the hands or hands without fingers
6. Diaphragmatic hernia

Suggestive signs (1 point)

1. Developmental deficit and/or cognitive deficit
2. Prenatal growth deficit
3. Postnatal growth deficit
4. Microcephaly
5. Small hands and/or feet
6. Fifth little finger
7. Hirsutism

The diagnosis of classic CdLS is defined by a score greater than or equal to 11, with at least 3 cardinal signs present. From 9 to 10 points, with at least 2 cardinal signs, the diagnosis of non-classical CdLS is established. If 4 to 8 points with at least 1 cardinal sign, molecular testing is indicated to confirm the diagnosis. If the score is less than 4 points, the molecular test is not indicated[3].

The patient in the report presented: meeting of the eyebrows in the midline and thick eyebrows, short and concave nose, long upper lip without furrow, oligodactyly in the hands, prenatal growth deficit, microcephaly, small hands and hirsutism, totaling 14 points; CdLS was diagnosed without the need for a molecular test.

After diagnosis of the syndrome, it is necessary to screen the child for malformations; an echocardiogram is requested, due to the high prevalence of congenital heart diseases, and renal USG. Imaging of the central nervous system is indicated in the presence of seizures[3].

In the case reported, the echocardiogram showed IAC without repercussions. Kidney and urinary tract USG scanS were normal. Testicles were located in the inguinal region. CT of the head, despite not being formally indicated at the time of diagnosis, was important to rule out other causes of multiple malformations.

There are specific growth and weight curves for monitoring children with CdLS, which should be used by the pediatrician who will care for the child[8,15], who should also advise parents that vaccination follows the usual vaccination schedule[3].

Feeding difficulties are present in many cases, and may have several causes, such as gastrointestinal malformations and difficulty in sucking, requiring a multidisciplinary approach, with the participation of a speech therapist[3,8]. Whenever possible, oral feeding should be maintained; however, in some cases GTT may be necessary[2,3,8].

CONCLUSION

Considering that CdLS has a rare incidence, case reports with literature review are an important source of data for approaching diagnostic and therapeutic experiences.

In this case, a NB with classic morphological characteristics of the disease was presented. Prenatal USG suggested congenital malformations and symmetric IUGR, but the diagnosis was defined after birth according to the clinical criteria recommended by the First International Consensus on the Diagnosis and Management of CdLS (2018), without the need for genetic testing. Considering a comprehensive approach to the patient and his family, it is necessary to consider the real benefit of a high-cost diagnostic test that does not alter prognosis and subsequent procedures.

The patient remains under outpatient follow-up. The childcare of these children is specific, according to their own growth and weight curves. Monitoring the psychomotor development and feeding difficulties in these patients is extremely important, and it is necessary to promote a multidisciplinary support which main objective is to improve quality of life.

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