v. 1, n. 1, 2021

International Journal of Health Science

Diagnostic overview of Cornelia de Lange Syndrome: a review

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Abstract: Objective: Present the pre- and postnatal diagnosis of Cornelia de Lange Syndrome (CdLS) and warn about its various clinical manifestations to improve the prognosis of affected patients. **Methods:** This is a literature review between the years 2010 to 2021, using the LILACS, MEDLINE, Pubmed and SciELO databases, using the descriptors "Cornelia de Lange Syndrome" and "Diagnosis". Original articles available in English, Portuguese and Spanish that responded to the objective of the study were included. 68 articles were reviewed among which 43.1% were case reports, 36.2% were bibliographic reviews and 20.7% were cohort studies. The studies expose topics ranging from prenatal diagnosis, genetic alterations, to the main manifestations of SCdL. **Conclusion:** It is concluded that SCdL has a broad phenotypic spectrum, its diagnosis is mostly made in the postnatal period and it is necessary that the syndrome is better contemplated in scientific circles and more widespread in the general population so that affected patients get better quality of life.
Keywords: Cornelia de Lange, Genetic Syndrome, Multidisciplinary approach, CdLS.

INTRODUCTION

Cornelia de Lange Syndrome (CdL) was first described by Brachmann in 1916 and later by Lange in 1933. It is a rare genetic condition with uncertain etiology, with an estimated incidence of 1:10,000 to 1:30,000 live births, an index of recurrence among siblings around 2 to 5% and the increasing prevalence due to the increase in diagnoses of individuals with mild forms of the disease (ANTONIE D. KLINE, et al., 2007).

However, the number of undiagnosed patients remains high, at around 20-30%, due to unrecognized causative genes, genetic mosaicism and multiplicity of phenotypic presentations (JUAN PIÉ, et al., 2016).

It is a congenital syndrome of autosomal dominant inheritance with incomplete penetrance, resulting from multiple alterations in the cohesin complex, responsible for chromatic cohesion, DNA repair and gene expression. Such alterations appear especially on chromosome 3, located in region 2q26.3, with a predominance associated with X. Currently, 7 genes have been associated with SCdL (NIPBL, SMC1A, SMC3, RAD21, HDAC8, BRD4, ANKRD11), and their mutations are responsible by about 70% of diagnosed cases (MUSINU KACARIA, et al., 2015).

Clinically broad, Cornelia de Lange Syndrome is seen as a phenotypic spectrum, involving the classical presentation and atypical presentation resulting from pathogenic variants in genes involved in the functioning of cohesin. It is classically characterized by intellectual impairment, distinct facial features, reduction and delay in growth and hirsutism. However, it can compromise any organ or system of the body, with multiple presentations and different phenotypes, making the earliest possible diagnosis, with a multidisciplinary and global approach is imperative to improve the care and attention to the individual with SCdL (ANTONIE D. KLINE, et al., 2018).

The present study aims to present, based on the synthesis of scientific evidence involving the diagnosis of SCdL, a warning to the reader about prenatal and postnatal diagnosis, neurobehavioral changes, genetic and immunological alterations. Also, present a flowchart of the diagnosis of this syndrome to guide clinicians to pay attention to the syndrome and change the expectations and care provided to patients.

METHODS

This is a qualitative research of articles searched in SciELO, LILACS, Pubmed and MEDLINE electronic databases. It gathered the scientific evidence published in the years 2010-2021. The electronic search was carried

out in June 2021 and the descriptors "Cornelia de Lange's Syndrome", "De Lange's Syndrome" and "Brachmann de Lange's Syndrome" were used.

The articles included were published in Portuguese, English and Spanish in the aforementioned period, addressing genetics, the clinical picture and diagnosis of SCdL, as well as the categories of literature review, cohort studies and case reports.

Articles that addressed different aspects of the clinical and diagnostic approach to the syndrome and articles that did not meet the inclusion criteria were excluded.

After the results found with the search strategy, the articles were sorted by titles by the researchers. Subsequently, those who fit into the study were evaluated by reading the abstracts. As a next step, the pre-selected articles were read in full, then classified as literature review, cohort study and case reports, later labeling them as the main subject in diagnosis, genetic study, alterations neurobehavioral, postnatal diagnosis, immunological alterations and causes of death.

RESULTS

A total of 68 articles were analyzed and 58 were classified as eligible to be included in the review. Among them, 51 (88%) were published in English, 4 articles (6.9%) in Spanish and 3 articles (5.1%) in Portuguese. Regarding the types of studies, 25 (43.1%) case reports, 21 articles (36.2%) are bibliographic reviews and 12 (20.7%) cohort studies, as shown in Graph 1.

As shown in Graph 2, 46.5% of the publications present the main genetic alterations found in SCdL. 20.6% of the studies present a diagnosis and alterations that occur in the prenatal period and 17.2% of the publications report on the main changes neurobehavioral. 6.8% of the analyzes describe the postnatal diagnosis. Only 1.72% of the studies call for some attention to immunological alterations. Also, 1.72% of the articles report on the causes of death.

The clinical suspicion and subsequent diagnosis of Cornelia de Lange Syndrome, therefore, is closely related to two moments: during prenatal care and/or early childhood, based on characteristic phenotypic alterations and genetic alterations. (ANTONIE D KLINE, et al., 2018)

The 2018 international consensus proposes that the diagnosis should be scored according to clinical and molecular variations, classifying the patient into typical and atypical. The scoring scheme assesses changes in basic characteristics, scoring two points for each item

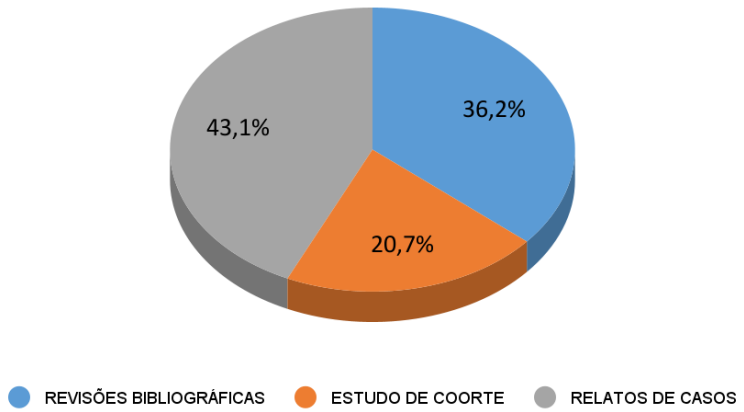


Gráfico 1 - Tipes of study

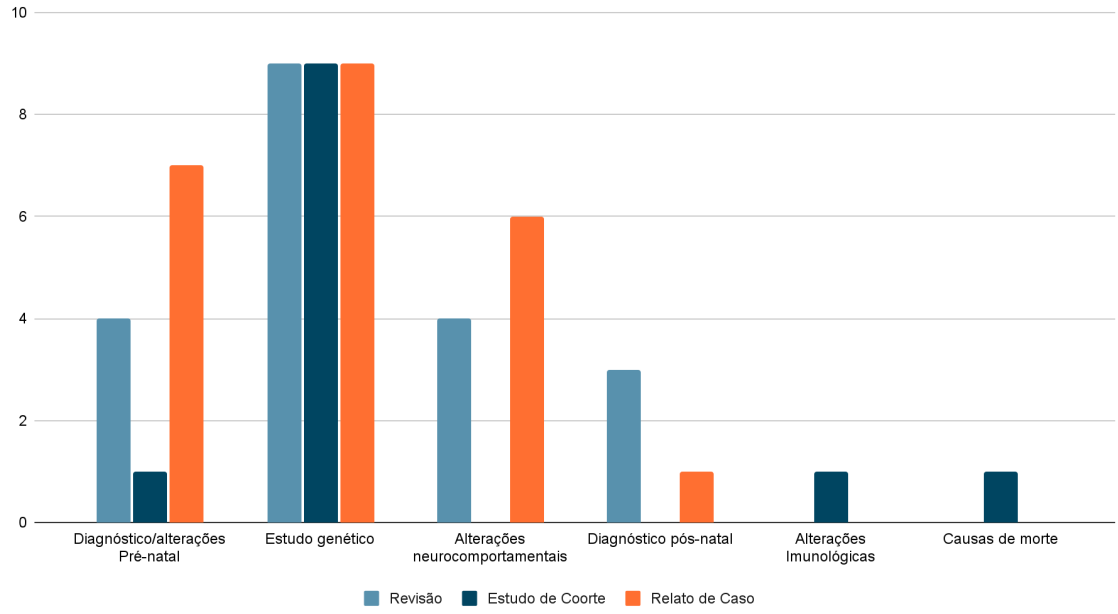


Gráfico 2 - Review, cohort study and case report

and suggestive characteristics, with one point for each marked attribute. (ANTONIE D KLINE, et al., 2018)

Cardinal features are composed of synophris and/or thick eyebrows; short nose/concave nasal crest/upturned nasal tip/thin upturned nostrils; thin upper lips/corners of mouth facing down; oligodactyly/adactyly; congenital diaphragmatic hernia. The suggestive ones integrate general developmental delay and/or intellectual disability; intrauterine growth restriction; postnatal growth retardation; microcephaly (pre and post natal); small hands and/or short feet; 5th short finger and presence of hirsutism, as shown in Table 1. (ANTONIE D KLINE, et al., 2018; LAURA AVAGLIANO, et al., 2017; L JACKSON, et al., 1993; MATTHEW A. DEADORFF, et al., 2020; PING ZHOU, et al., 2020)

The tables below were built based on the guidelines presented in the 2018 consensus that assesses the cardinal signs and scores them to guide the diagnosis of Cornelia de Lange Syndrome, in order to facilitate data analysis. (ANTONIE D KLINE, et al., 2018)

The patient classified as typical has a score greater than or equal to 11 points and has at least 3 cardinal features; the atypical patient scores from 9 to 10 and must have at least 2 cardinal features; for a score between 4 and 8 with only one cardinal characteristic, the molecular test is indicated; and a score lower than 4 is not indicated for molecular testing, as shown in table 2 (ANTONIE D KLINE, et al., 2018).

Genetic variations can be deletions, microdeletions or translocations. However, the mechanism is not fully understood. The first protein to be correlated with the SCdL spectrum is NIPBL, classified as a protein that carries a classic disease phenotype. The other proteins associated with the syndrome (SMC1A, SMC3, RAD21, HDAC8, BRD4, ANKRD11) are related to milder spectra of the disease, which makes its diagnosis and early management difficult, necessary for a better prognosis (PATRIZIA SAROGNI, et al., 2020; LINDA MANNINI, et al., 2013; MARTHA AND LOPEZ-BURKS, et al., 2016; LAURA AVAGLIANO, et al., 2017).

características cardinais	pontuação
sinófris e/ou sobrancelhas grossas	2
nariz curto, crista nasal côncava e/ou nariz arrebitado	2
sulco nasolabial longo e/ou liso	2
lábio superior fino e/ou cantos da boca voltados para baixo	2
oligodactilia ou adactilia	2
hérnia diafragmática congênita	2
características sugestivas	
atraso de desenvolvimento e/ou deficiência intelectual	1
atraso de crescimento pré-natal	1
atraso de crescimento pós natal	1
microcefalia pré ou pós natal	1
mãos pequenas e/ou pés curtos	1
5º quirodáctilo curto	1
hirsutismo	1

conduta
≥ 11 pontos dos quais ao menos 3 são cardinais: SCdL clássica
9 – 1 pontos dos quais ao menos 2 são cardinais: SCdL não clássica
4-8 pontos dos quais ao menos 1 é cardinal: proceder a testes moleculares
< 4 pontos: critérios insuficientes para diagnóstico de SCdL

Prenatal diagnosis is infrequent, as SCdL is a rare genetic syndrome when compared to others. The fetal phenotype presented by ultrasound may show some suggestive changes such as intrauterine growth restriction, increased nuchal translucency, both asymmetrical and bilateral limb abnormalities, facial abnormalities, hypertrichosis and polyhydramnios may be evidenced (LAURA AVAGLIANO, et al., 2017; E; . SPAGGIARI, et al. 2013; E. THELLIER, et al., 2017).

The measurement of placental protein associated with maternal serum pregnancy (PAPP-A), which is a glycoprotein produced by the placenta, may be a predictor for SCdL in the first and second trimester of pregnancy, as in cases reported in the literature of the syndrome, its serum level is reduced, but it is necessary that the test is available everywhere and that it is implemented in the prenatal routine (LAURA AVAGLIANO, et al., 2017; DINAH M. CLARK, et al., 2012; MARÍA CONCEPCIÓN GIL-RODRÍGUEZ, et al., 2015).

According to the 2018 consensus diagnostic criteria, topics that can be seen in the prenatal period and classified as cardinal features are facial and limb abnormalities, and suggestive features include intrauterine growth restriction and the presence of hirsutism. All these attributes, in order to make the diagnostic score, require an imaging exam, such as ultrasound, which is operator-dependent and needs to be available to all pregnant women. According to the Ministry of Health, in Brazil the ultrasound exam is not mandatory in prenatal care in low-risk pregnancies, so the possibility or early diagnosis of the syndrome are far from reality (BRASIL, 2012).

Molecular sequencing should be performed when the syndrome is suspected both prenatally and after birth, in the presence of a score between 4 and 8, and when there is a positive family history for the syndrome. The genetic test will show the panel of genes already known for SCdL, showing the presence or absence of variants that reproduce the syndrome findings (MORAD ANSARI, et al., 2014; MINGYAN HEI, et al., 2018; BO YUAN, et al., 2015).

According to the 2007 consensus, genetic mapping was not mandatory and was characterized as having little diagnostic value, thus, the patient's phenotype was more prioritized. Nowadays, broad molecular tests are more required for their better genetic description and for the search for yet unknown genes and those that give milder characteristics of the disease (PING ZHOU, et al., 2020; MINGYAN HEI, et al., 2018).

According to the 2007 and 2018 consensus, the most prevalent SCdL gene is the NIBPL, which is described in the literature and has been proven to have variants that are associated with more severe cases and with greater involvement in limb alterations. Deletion, mosaicism and duplication events in this gene do not change the way the syndrome presents itself. Other genes already studied and confirmed for SCdL (SMCA1, SCMC3, RAD21, BRD4, HDAC8 and ANDK11) also express SCdL, but with milder phenotypes, so the diagnosis can be sometimes imperceptible (NIZON M., et al., 2016; MARÍA E. TERESA-RODRIGO, et al., 2014).

The availability of sequencing depends on financial factors, which can determine what type of technology the healthcare provider has for the diagnosis of the syndrome. For individuals with a classic presentation, the phenotype allows physicians to make a more accurate diagnosis, whereas those with less typical gene expressions and thus, milder phenotypes, may go unnoticed and receive inadequate treatment or even not obtain it. (YU-WEI CHENG, et al., 2014; SILVIA RUSSO, et al., 2012).

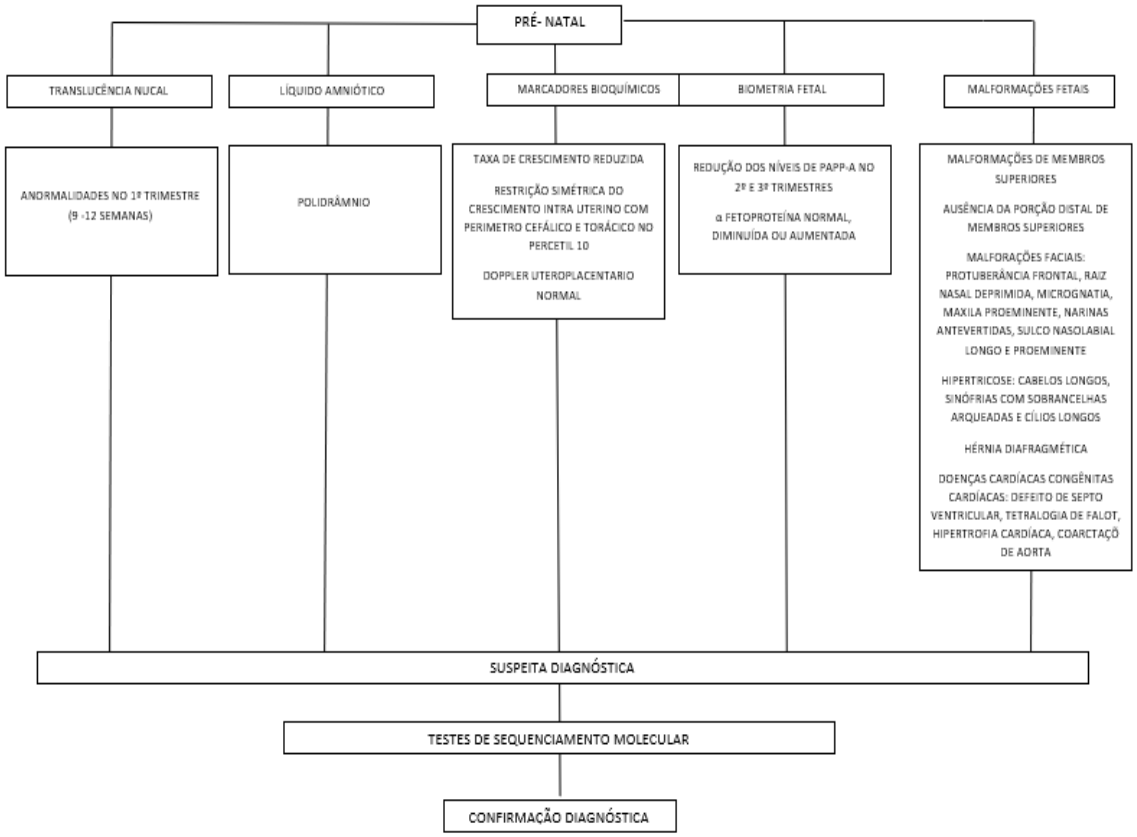
Thus, the following flowchart, built based on the consensus information presented abo-

ve, exposes a baseline for clinical suspicion during prenatal care, listing the main findings of this period that suggest the presence of SCdL and that require further diagnosis. (ANTONIE D KLINE, et al., 2018)

The Cornelia de Lange Syndrome, in addition to showing the cardinal and suggestive alterations mentioned above, can cause multiple systemic alterations. The occurrence of gastrointestinal malformations may be part of the manifestations of SCdL, often incurring in esophageal atresia, Meckel's diverticulum, imperforate anus and pyloric stenosis. Cecal volvulus and constipation may affect a smaller proportion of individuals, while diarrhea, flatulence and lactose intolerance are quite common. Gastroesophageal reflux is the most common gastrointestinal manifestation, affecting patients with SCdL since childhood and leading to complications such as pneumonia, eating difficulties, developmental changes, weight gain, agitation and sleep difficulties. (WICK M. et al., 1982, CUNNIF, C. et al. 1993, HOUSAIN, K. et al., 1994, CHRIER, S. et al., 2011).

In addition to the classic picture of synophris, full eyebrows and long eyelashes, unilateral or bilateral ptosis, blepharitis and obstruction of the lacrimal duct, besides visual acuity changes, nystagmus and strabismus, can be found. (YAN, J et al. 2006, WYGNANSKI-JAFFE, T et al, 2005, NALLASAMY, S et al, 2006, AVIGITDOU, G et al, 2015)

The inner ear ossicles can present malformations and hearing loss is common, typically bilateral and can vary from mild to severe impairment. Acutely, otitis and sinusitis can occur at all stages of life. (STALOFF, R et al., 1990, SASAKI, T et al, 2008, MARCHISIO, P, et al, 2008, MARCHISIO, P et al, 2014, JANEK, K. et al, 2002)



Musculoskeletal malformations affect mostly the upper limbs and more frequently in males. Small hands, missing forearm, fusion of radius and ulna, and oligodactyly may occur. Lower limb malformations are rare. (HOUISMAN, S. et al, 2017, GILIS, L. et al, 2004, MEHTA, D. et al 2016, ROPOSCH, A. et al, 2004, BARBONI, C. et al. , 2012).

Neurological conditions such as seizures and epilepsy are common and start early, in addition to sleep difficulties, sleep apnea, insomnia and difficulty staying awake during the day. Cognitive alterations can range from mild to severe impairment, leading to difficulties in understanding sensory stimuli, impaired adaptive behavior with the presence of self-mutilation and aggressive attitudes, and stereotyped and repetitive actions (KLINE, A. et al, 2018, VERROTTI, A. et al, 2013, ZAMBRELLI, J. et al, 2016, BOGDASHINA, O., et al, 2016, OLIVER, C., et al, 2009, RICHARDS, C. et al, 2015, LEEKAM, S. et al, 2011).

CONCLUSION

The multiple consequences of SCdL make multidisciplinary care and individualized attention to the patient imperative, with care directed to each of the symptoms. Early and continued diagnosis are the keys to the quality of life of individuals with SCdL. Thus, it is imperative that clinical suspicion is always present when considering the characteristic prenatal, postnatal and genetic alterations. Early and comprehensive care and individualized clinical management are the keys to providing individuals with Cornelia de Lange Syndrome with quality of life.

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