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Gastrointestinal Manifestation in Brazilian Cornelia De Lange Patients

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1. Introduction

Cornelia de Lange Syndrome (CdLS) is a rare genetic disease (OMIM #122470, #300590, #300882, #614701, #610759), with a broad phenotypic spectrum, including congenital malformations, neurodevelopmental delay, intellectual disability, and behavioral disorders [1,2]. The first description of the disease was made by a Dutch pediatrician, Cornelia de Lange, in 1933.2 In its classic form, CdLS is characterized by facial dysmorphisms, short stature, hirsutism, upper limb defects, intellectual disability, and behavioral disorders, including self-injury, anxiety, autistic characteristics, and sleep problems [1,3]. Other common findings include congenital heart disease, gastroesophageal reflux disease (GERD), sensorineural deafness, myopia, and cryptorchidism in boys [1,2]. The prevalence is estimated to be between 1 in 10,000 and 1 in 30,000 live births [4]. Variants in the NIPBL gene are the most common cause of CdLS and represent approximately 80% of cases. Furthermore, a substantial number of individuals with classic CdLS (up to 20%) have mosaic NIBPL variants [2,56]. Other subunits or regulators of the complex (SMC1A, SMC3, RAD21, and HDAC8) are responsible for 10–15% of cases [7,8]. Variants in additional cohesin-associated proteins, such as MAU2, STAG1, and STAG2, have been associated with CdLS or phenotypes resembling CdLS in a few individuals [2]. Although gastrointestinal (GI) disorders are common in CdLS patients, there are few specific studies about this subject, most of them case reports [9-18]. The aim of this study is to describe and characterize gastrointestinal malformations, signs, and symptoms in 56 molecularly diagnosed CdLS Brazilian patients.

2. Methods

All patients were submitted to a clinical and molecular evaluation, which included clinical findings, pedigree, physical examination, photographic documentation, and review of medical records. The molecular confirmation was done by Whole Exome Sequencing (WES) from DNA extracted from peripheral blood or buccal cells or RNA-Seq from total RNA isolated from lymphoblastoid cell lines (LCLs). All patients were evaluated at Instituto da Criança between March 2017 and November 2024.

2.1. The Following Specific Data Have Been Collected:

-CdLS score by Kline 2018 [2].

-Auxological data: Growth parameters (weight and height) have been plotted on standard growth charts and CdLS growth charts. Body mass index (BMI) is a calculation of a body person's weight (in kilograms) divided by the square of their height (in meters). Currently, there are no accepted cutoffs for BMI below 2 years old. In this group, we plot the weight-for-recumbent length graph. BMI categories for children or adolescents >2 years of age are underweight, for BMI < 5th percentile, healthy weight, for BMI >= 5th percentile to < 85th percentile, overweight, for BMI >= 85th to < 95th percentile,

and obesity, for BMI >= 95th percentile. For adults 20 and older, BMI are: underweight if less than 18.5, healthy weight18.5 to less than 25, overweight 25 to less than 30, and obesity 30 or greater [19].

-Use of nutritional devices (type, age of introduction and duration of its use).

-Presence of gastrointestinal disorders and its treatment.

3. Results

Our cohort consists of 56 CdLS molecularly diagnosed patients by WES or RNA-Seq (23 females and 33 males, mean age 11,1 yo, median 7,5 yo, range 6 mo to 43 yo). NIPBL variants were found in 51 patients (91%) and SMC1A variants were found in 5 (9%). One male patient died due to an infectious respiratory cause during the COVID-19 pandemic. According to the CdLS score2, 44 (78%) patients were classified as classical phenotype, 6 (11%) non-classical and, 6 (11%) had molecular testing indication. Prenatal-onset growth failure is present in most individuals with CdLS. In our cohort, it was present in 43 (77%) patients. Failure to thrive, that is, difficulty gaining weight and height as a child, was described by 51 (91%) parents. Growth retardation was noted in 42 (75%) patients when compared to standard growth curves but only in 7 (12%) patients when specific growth charts for CdLS were used. BMI calculation in our cohort showed that 22 (39%) patients were underweight, healthy weight was evident in 22 (39%) patients, and conditions of overweight/ obesity were present in 12 (22%) patients.

A very common characteristic was feeding difficulties in early childhood, present in 46 (80%) patients. Of these, 19 (41%) used a nutritional device; a nasogastric tube (NGT) was used in 18 cases, and percutaneous endoscopic gastrostomy (PEG) in 5. Regarding PEG use, 2 positioned it within the first year of life while 3 positioned it after. Three patients keep PEG in place with a medium period of use of this device of 18 months. Only two patients persist with PEG after 3 and 11 years of use. The main cause of hospital admissions in our cohort was gastrointestinal problems and included recurrent pneumonia in 10 cases, diarrhea (4 cases), non-responsive to medication gastroesophageal reflux disease (GERD) (2 cases), colon rupture (1 case) and melena (1 case). In relation to surgery, eight patients were submitted to gastric fundoplication, five patients to herniorrhaphy (one emergency), five patients to gastrostomy, three patients to hiatoplasty and gastric fundoplication, two patients to Meckel diverticulectomy, two patients submitted to Barrett's Esophagus procedures, one patient submitted to colostomy due to colon rupture, one patient to cholecystectomy, one patient submitted to surgical procedure for cecal volvulus, and one patient to pyloromyotomy. Gastrointestinal disorders were noted in 48/56 (86%) patients. Gastroesophageal reflux disease was the most common diagnosis, affecting 45 (80%) of the patients. Still, 12 patients are receiving ant reflux medications. Other diagnoses included cleft palate (12%), inguinal hernia (10%), esophagitis (5%), hiatal hernia (5%), constipation (5%), Meckel's diverticulum (3%), esophageal stenosis (3%), pyloric stenosis (3%), diarrhea (2%), Barrett's esophagus (2%), biliary lithiasis (2%), and umbilical hernia (2%).

4. Discussion

It is well-known that patients with CdLS have an increased incidence of GI disorders. Our study is the first one done only with molecular confirmed patients. Small for gestational age was seen in 77% of the cases. It confirms the importance of considering a feeding team evaluation just after birth, including aspiration risk, and gastric tube placement if necessary. Feeding difficulties is almost universally present, and it was a concern for 80% of our cohort. Recommended treatment involves feeding therapy and gastrostomy tube may be required if persistent feeding issues. Our data agrees with the literature which demonstrates that 40% of the CdLS patients used nutritional devices [2,17]. The most frequent GI disorder found in our cohort - gastroesophageal reflux disease (GERD)- is in accordance with the consensus. In studies, up to 75% of patients are detected with GERD, and our study found an even higher incidence (80%). GERD may become apparent in variable manner, including feeding problems, recurrent (chemical) pneumonias, failure to thrive, agitation, restlessness or poor sleep. In our cohort hospitalization due to recurrent pneumonia was the most common. Since GERD is the most prevalent and severe gastrointestinal problem and can present in infancy proactive management is recommended [2,20]. Congenital diaphragmatic hernia (CDH) has been diagnosed both pre- and postnatally, but may be under ascertained, especially in infants who die in the perinatal period. We did not have any case in our cohort [20]. Growth disorder was noted in 75% of the patients, although weight and height were within the normal limits in the majority using the specific growth charts for CdLS. If growth velocity is lower than expected, gastrointestinal problems, thyroid dysfunction and growth hormone disturbances should be considered [2].

5. Conclusion

Our survey demonstrates that Individuals with CdLS have more frequent gastrointestinal concerns and malformations, and with time the great majority of patients succeeded in achieving a normal oral nutrition. Gastroesophageal reflux disease (GERD) is frequent and should be ruled out as the cause of different manifestations, especially in patients with poor communication.

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