Journal of Pediatric Surgery xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Cornelia de Lange syndrome and congenital diaphragmatic hernia☆,☆☆,★

Vikas S. Gupta [a], Amir M. Khan [b], Ashley H. Ebanks [a], Pamela A. Lally [a], Kevin P. Lally [a], Matthew T. Harting [a,*], for the Congenital Diaphragmatic Hernia Study Group

[a] Department of Pediatric Surgery, McGovern Medical School at the University of Texas Health Science Center and Children's Memorial Hermann Hospital, Houston, TX
[b] Department of Pediatrics, McGovern Medical School at the University of Texas Health Science Center and Children's Memorial Hermann Hospital, Houston, TX

ARTICLE INFO

Article history:
Received 22 April 2020
Received in revised form 3 June 2020
Accepted 4 June 2020
Available online xxxx

Key words:
Congenital diaphragmatic hernia
CDH study group
Cornelia de Lange syndrome
Brachmann de Lange syndrome
Outcomes

ABSTRACT

Purpose: There is a known association between Cornelia de Lange syndrome (CdLS) and congenital diaphragmatic hernia (CDH), with CDH being the cause of death in 5%–20% of CdLS cases. We aimed to identify and describe patients with CDLS and CDH. We hypothesized that CdLS would be associated with high-risk CDH and poor outcomes.
Methods: CDH Study Group patients from 1995 to 2019 were included. Those with CdLS were reviewed retrospectively. Rates of repair and outcomes were compared between patients with and without CdLS.
Results: We identified 9,251 CDH patients. Of those, 21 had confirmed CdLS. CdLS patients had a lower birth weight (2.2 ± 0.57 kg) than non-CdLS patients (2.9 ± 0.64 kg) ($p<0.001$). 5-min Apgar scores were lower in CdLS patients (6, 4–7) than non-CdLS patients (7, 5–8) ($p=0.014$). Only 33% of CdLS patients underwent diaphragmatic repair compared to 84.2% of non-CdLS patients ($p<0.001$). Mortality was 76% for CdLS patients compared with 29% for non-CdLS patients ($p<0.001$). Of the 7 CdLS patients who underwent repair, 5 survived to hospital discharge.
Conclusions: Infants with CdLS and CDH have a poor prognosis. However, CdLS patients who undergo repair can survive to discharge; therefore, the concomitant diagnosis of CdLS and CDH is not necessarily a contraindication to repair. Early recognition of these anomalies can assist with counseling and prognostication.
Type of study: Retrospective comparative study
Level of evidence: III

© 2020 Elsevier Inc. All rights reserved.

First described in 1933, Cornelia de Lange syndrome (CdLS) is a constellation of genetic abnormalities classically including limb malformations, dysmorphic facies, and developmental delay [1]. It is estimated to affect one in every 10,000 to 30,000 live births, though its incidence is likely underreported owing to high variability in presentation [1]. The developmental pathobiology of CdLS is unclear, but it has been linked to abnormalities in genes affecting chromatin regulation [2]. Absent of severe cardiopulmonary or gastrointestinal malformations, patients with CdLS generally have a near-normal life expectancy [3].

Congenital diaphragmatic hernia (CDH), a developmental anomaly in which infants are born with a diaphragmatic defect, affects one in every 2,500 to 3,000 newborns [4]. The underlying embryogenesis of CDH remains incompletely understood, though numerous maternal and neonatal risk factors have been identified as potential contributors to CDH development, and the fundamental mechanism is currently believed to be multifactorial. Despite this heterogeneity, up to 30% of CDH cases have identifiable genetic anomalies such as chromosomal defects or single-nucleotide variants [5].

The association between CdLS and congenital diaphragmatic hernia (CDH) is well described in the literature. CDH is present in 5%–20% of cases of CdLS and is the reported cause of death in as many as 40% of neonatal CdLS fatalities [6]. Despite this known association, data on patients with both CDH and CdLS are limited to individual reports or small case series. To date, the largest study of this population, published in 1993, included 12 patients, 11 of whom died [7]. Since that time, there have been advances in both detection of CdLS and management of CDH, such that our ability to care for these patients may have improved.

Given the lack of data surrounding this population, our objective was to identify the characteristics, management, and outcomes of patients with concomitant CdLS and CDH. We hypothesized that CdLS would be associated with severe, high-risk CDH and poor outcomes.

☆ Disclosure: Authors have no relevant financial conflicts of interest.
☆☆ Sources of support: None.
★ Acknowledgments: Ladybug Foundation, Men of Distinction Foundation.
* Corresponding author at: Department of Pediatric Surgery, University of Texas McGovern Medical School, Houston, 6431 Fannin St, MSB 5.233, Houston, TX 77030. Tel.: +1 713 500 7300 (o).
E-mail address: matthew.t.harting@uth.tmc.edu (M.T. Harting).

https://doi.org/10.1016/j.jpedsurg.2020.06.003
0022-3468/© 2020 Elsevier Inc. All rights reserved.

Please cite this article as: V.S. Gupta, A.M. Khan, A.H. Ebanks, et al., Cornelia de Lange syndrome and congenital diaphragmatic hernia, Journal of Pediatric Surgery, https://doi.org/10.1016/j.jpedsurg.2020.06.003

1. Methods

1.1. Registry data and inclusion criteria

Patient data were retrieved from the Congenital Diaphragmatic Hernia Study Group (CDHSG) registry. The CDHSG is a multicenter collaboration initiated in 1995 that compiles data on all live-born CDH infants from more than 85 participating institutions, both in the US and abroad. Data collected include patient demographics, characteristics such as cardiac and chromosomal abnormalities, and in-hospital outcomes. Centers are directly contacted to validate and to gather missing information to ensure high-fidelity data collection. The CDHSG is approved by the University of Texas McGovern Medical School at Houston Center for the Protection of Human Subjects/Institutional Review Board (#HSC-MS-03-223; Ref #118886). For this analysis, data were queried for all patients in the CDHSG registry from 1995 to 2019. Patients with a chromosomal abnormality of "Cornelia de Lange" or "Brachmann de Lange" syndrome were analyzed. Patients with multiple possible chromosomal abnormalities (example: "Donnai–Barrow syndrome vs Cornelia de Lange syndrome") were not counted as having CdLS.

1.2. Statistical analysis

Rates of repair and outcomes were compared between patients with and without CdLS. Categorical data were compared using Pearson's Chi-Squared test; continuous data were compared with the Kruskal–Wallis analysis. All analyses were performed using Stata/IC version 16.0 (Stata Corp LP, College Station, Texas) and Prism 8 (San Diego, California).

2. Results

2.1. Patient characteristics

We identified 9,251 infants with CDH. Of these, 585 (6.3%) patients were diagnosed with at least one chromosomal abnormality, and 21 (0.23%) infants were diagnosed with CdLS. Overall, patients with CdLS were born earlier (median 37 weeks of gestation, IQR 36–38 weeks), compared to patients without CdLS (median 38 weeks of gestation, IQR 37–39 weeks; $p<0.04$). CdLS patients were more likely to be inborn (81%) compared to non-CdLS patients (50%) ($p=0.005$), and birth weight was lower in CdLS patients (median 2.2 kg, IQR 1.8–2.6) compared to patients without CdLS (median 3.0 kg, IQR 2.6–3.4; $p<0.001$). Patients with CdLS had lower Apgar scores at 5 minutes (median 6, IQR 4–7) compared to patients without CdLS (median 7, IQR 5–8; $p=0.02$). Rates of major cardiac abnormality (without CdLS 8%, with CdLS 10%, $p=0.76$) and rate of left-sided diaphragmatic defects (without CdLS 83%, with CdLS 76%, $p=0.42$) did not vary significantly between the groups. These data are summarized in Supplementary Table 1.

2.2. Repair rates and outcomes

The use of extracorporeal life support (ECLS) was similar between the patients with CdLS (24%) and without CdLS (30%) ($p=0.57$) (Fig. 1). Overall mortality was higher in CdLS patients (76%) compared to patients without CdLS (29%) ($p<0.001$). CdLS patients had more early deaths (within first 48 h of life) compared to patients without CdLS (57% vs. 8.5% respectively, $p<0.001$). Of the 21 patients with CdLS, 7 (33%) underwent operative repair, compared to 84% of the non-CdLS group ($p<0.001$). Despite the different rates of repair, survival to hospital discharge after surgery was comparable between groups (71% in CdLS, 84% in non-CdLS; $p=0.36$). Of the 5 patients with CdLS who survived to discharge, the median length of hospital stay (LOS) (116 days, IQR 116–131, range: 62–323) was longer than that of survivors without CdLS (36 days, IQR 22–67) ($p=0.002$). Characteristics of CdLS nonsurvivors and survivors are listed in Supplementary Tables 2 and 3, respectively.

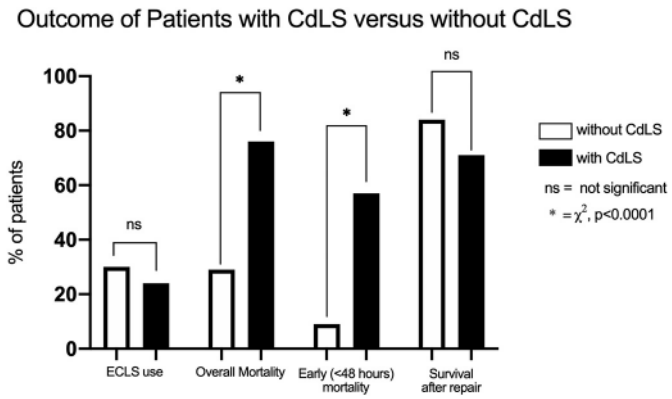

Fig. 1. Outcome of CdLS patients versus non-CdLS patients.

2.3. Sensitivity analysis

Among patients in the CDHSG, patients who were listed as having multiple *possible* chromosomal abnormalities (example: "Donnai–Barrow syndrome vs Cornelia de Lange syndrome") were not counted as having CdLS. In order to make sure exclusion of these patients did not greatly alter our results, a sensitivity analysis was performed. When including even these nonconfirmed cases of CdLS, 35% of CdLS patients underwent repair compared to 85% of the non-CdLS group ($p<0.001$), and overall mortality remained higher in CdLS patients (77%) compared to non-CdLS patients (29%) ($p<0.001$). The use of ECLS remained similar between CdLS and non-CdLS patients (19% vs 30%, respectively) ($p=0.25$)

3. Discussion

Family counseling about CDH or CdLS individually can be challenging, given the wide variety of phenotypes and outcomes for these two pathologies. When the diagnoses are combined, it serves to further obfuscate the potential clinical course, given the lack of data regarding patient outcomes. We present a large series of patients with concomitant CDH and CdLS, a rare combination. In 1993, Cunnif et al. reported a series of 12 patients, focusing their analysis primarily on the manifestations of CdLS (extremity malformation type and location, karyotype) [7]. As in our population, one-third of the patients in that study underwent operative repair. This result is striking given that, despite the advances in neonatal critical care, genetic testing, and operative techniques in CDH in the more than a quarter century since that original series, the repair rate has remained unchanged.

Multiple factors likely contribute to the low rate of operative repair in patients with both CDH and CdLS. Our data show that these patients represent a sicker patient population at birth, likely rendering some patients impossible to stabilize. Among our cohort, more than half of CdLS patients died within the first 48 hours of life, suggesting that early mortality was high, usually without aggressive intervention measures such as ECLS or surgical repair (Supplementary Table 2). Notably, although impossible to quantify given these data, it is likely that, at least for some nonrepaired patients, families/physicians elected to forego aggressive resuscitation, ECLS, and/or surgical diaphragmatic repair. Our dataset lacks the granularity to elucidate which families were offered ECLS and/or repair and declined, but, in other reports of CDH and CdLS, families, when counseled about the prognosis, frequently declined surgical intervention [7].

Early diagnosis and recognition of CdLS are critical for clinical decision making and family counseling. CdLS is a primarily clinical diagnosis based on the presence of cardinal features (one of which is CDH) and

Please cite this article as: V.S. Gupta, A.M. Khan, A.H. Ebanks, et al., Cornelia de Lange syndrome and congenital diaphragmatic hernia, Journal of Pediatric Surgery, https://doi.org/10.1016/j.jpedsurg.2020.06.003

ARTICLE IN PRESS

Table 1
Classic and suggestive features of CdLS.

Classic features	Suggestive features
Thick eyebrows or synophrys	Developmental delay or intellectual disability
Long or smooth philtrum	Pre or postnatal growth retardation
Short nose, concave nasal ridge, or upturned nasal tip	Pre or postnatal microcephaly
Thin upper vermilion or downturned corners of mouth	Small hands and/or feet
Hand oligodactyly and/or adactyly	Short fifth finger
Congenital diaphragmatic hernia	Hirsutism

suggestive features (Table 1) [8]. Patients with a "classic" CdLS phenotype can be diagnosed without identification of a particular genetic variant, whereas patients with suspected CdLS or a suspicious phenotype should undergo genetic testing [8]. Despite our increasing ability to diagnose and characterize CdLS, severity scoring and prognostic algorithms are still lacking [8]. Prenatal investigation for CdLS is indicated when other features concerning for CdLS are noted prenatally, such as limb anomalies or abnormal fetal facial profile [8]. One report of 53 CdLS patients showed a prenatal diagnosis of CDH in 30% of cases [9]. Emerging evidence suggests that certain genetic variants present with more severe CdLS phenotypes than others [2]. In the future, identification of CDH in patients with milder versions of CdLS may enable us to identify operative candidates, allowing more informed counseling for families [5].

Longitudinal reports of CDH-survivors with CdLS are lacking. Without critical organ system anomalies (cardiac malformations, gastrointestinal anomalies), most CdLS patients can be expected to survive into adulthood [8]. Similarly, CDH has an overall survival of around 70%, and most patients will survive into adulthood [10]. Critical to the long-term care of patients with CDH, CdLS, or both is the establishment of a multidisciplinary follow-up team that can provide the necessary complex care these patients require [11].

There are obvious limitations to this study. Our cohort of CdLS patients, despite being the largest reported in the literature, remains small, at only 0.2% of patients from the CDHSG. This number is almost certainly underreported, given the diagnostic difficulty of CdLS, particularly before the advent of advanced genotyping techniques. Given that the CDHSG is a voluntary registry, it has a limited ability to capture highly specific details about patient characteristics and medical decision making. Additionally, given that the size of the diaphragmatic defect (CDHSG stage) is determined at the time of the operation, defect size data were only available for one-third of CdLS patients (Supplementary Tables 2 and 3). While prenatal imaging markers are emerging as adjunct predictors of defect size, these data were not available for our cohort of patients. This limited our ability to do comparative analyses using defect size as a risk stratifier, and we stratified by other conventional markers such as 5-min Apgar and birth weight.

In conclusion, a diagnosis of Cornelia de Lange syndrome should not be considered an absolute contraindication to operative repair of a congenital diaphragmatic hernia. Many of these patients are critically ill at birth and will not survive past the first 48 hours of life. However, a subset of patients will not only tolerate repair, but also survive until discharge, although our data suggest a longer hospital stay for these patients. Heterogenous genotypic abnormalities among CdLS patients lead to variable presentation, different associated anomalies, and, ultimately, a broad spectrum of possible prognoses. While our dataset does not capture the detailed characteristics of each patient with both CDH and CdLS, there may be a subset of patients with favorable demographics that should be offered aggressive resuscitative critical care, ECLS, and surgical repair. All patients with CdLS should be closely evaluated for the presence of CDH, and, conversely, all patients with CDH should prompt suspicion for CdLS. Early diagnosis and recognition of both pathologies can be a critical component of the care and outcome of these patients and can also help in family counseling and decision-making.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpedsurg.2020.06.003.

Acknowledgments

This work was supported by the Men of Distinction, Houston, TX and the Ladybug Foundation, Portland, OR.

References

[1] Liu J, Krantz ID. Cornelia de Lange syndrome, cohesin, and beyond. Clin Genet. 2009;76(4):303–14.
[2] Avagliano L, Parenti I, Grazioli P, et al. Chromatinopathies: a focus on Cornelia de Lange syndrome. Clin Genet. 2020;97(1):3–11.
[3] Kline AD, Grados M, Sponseller P, et al. Natural history of aging in Cornelia de Lange syndrome. Am J Med Genet C Semin Med Genet. 2007;145C(3):248–60.
[4] Greer JJ. Current concepts on the pathogenesis and etiology of congenital diaphragmatic hernia. Respir Physiol Neurobiol. 2013;189(2):232–40.
[5] Kardon G, Ackerman KG, McCulley DJ, et al. Congenital diaphragmatic hernias: from genes to mechanisms to therapies. Dis Model Mech. 2017;10(8):955–70.
[6] Schrier SA, Sherer I, Deardorff MA, et al. Causes of death and autopsy findings in a large study cohort of individuals with Cornelia de Lange syndrome and review of the literature. Am J Med Genet A. 2011;155A(12):3007–24.
[7] Cunniff C, Curry CJ, Carey JC, et al. Congenital diaphragmatic hernia in the Brachmann–de Lange syndrome. American Journal Of Medical Genetics. 1993;47(7):1018–21.
[8] Kline AD, Moss JF, Selicorni A, et al. Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement. Nat Rev Genet. 2018;19(10):649–66.
[9] Clark DM, Sherer I, Deardorff MA, et al. Identification of a prenatal profile of Cornelia de Lange syndrome (CdLS): a review of 53 CdLS pregnancies. Am J Med Genet A. 2012;158A(8):1848–56.
[10] Harting MT, Lally KP. The Congenital Diaphragmatic Hernia Study Group registry update. Semin Fetal Neonatal Med. 2014;19(6):370–5.
[11] Tan JK, Banton G, Minutillo C, et al. Long-term medical and psychosocial outcomes in congenital diaphragmatic hernia survivors. Arch Dis Child. 2019;104(8):761–7.

Please cite this article as: V.S. Gupta, A.M. Khan, A.H. Ebanks, et al., Cornelia de Lange syndrome and congenital diaphragmatic hernia, Journal of Pediatric Surgery, https://doi.org/10.1016/j.jpedsurg.2020.06.003