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Causes of Death and Autopsy Findings in a Large Study Cohort of Individuals with Cornelia de Lange Syndrome and Review of the Literature

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Abstract

To identify causes of death (COD) in probands with Cornelia de Lange syndrome (CdLS) at various ages, and to develop guidelines to improve management and avoid morbidity and mortality, we retrospectively reviewed a total of 426 probands with confirmed clinical diagnoses of CdLS in our database who died in a 41-year period between 1966–2007. Of these, 295 had an identifiable COD reported to us. Clinical, laboratory and complete autopsy data were completed on 41, of which 38 were obtainable, an additional 19 had autopsies that only documented the COD, and 45 probands had surgical, imaging, or terminal event clinical documentation of their COD. Proband ages ranged from fetuses (21 to 40 weeks gestation) to 61 years. A literature review was undertaken to identify all reported causes of death in CdLS individuals.

In our cohort of 295 probands with a known COD, respiratory causes including aspiration/reflux and pneumonias were the most common primary causes (31%), followed by gastrointestinal disease, including obstruction/volvulus (19%). Congenital anomalies accounted for 15% of deaths and included congenital diaphragmatic hernia and congenital heart defects. Acquired cardiac disease accounted for 3% of deaths. Neurological causes and accidents each accounted for 8%, sepsis for 4%, cancer for 2%, renal disease for 1.7%, and other causes, 9% of deaths. We also present 21 representative clinical cases for illustration.

This comprehensive review has identified important etiologies contributing to the morbidity and mortality in this population that will provide for an improved understanding of clinical complications, and management for children and adults with CdLS.

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Keywords

Cornelia de Lange Syndrome; Brachmann de Lange Syndrome; causes of death; mortality; autopsy; CdLS

INTRODUCTION

The Cornelia de Lange Syndrome (CdLS) (OMIM# 122470, 300590, 610759) is a dominantly inherited multi-system developmental disorder characterized by growth delay, intellectual disability, gastroesophageal dysfunction and structural differences including; upper limb, cardiac, ocular, genitourinary anomalies as well as characteristic facial features and hypertrichosis. CdLS is genetically heterogeneous, caused by mutations in *NIPBL* (approximately 50% of cases), *SMC1A* (approximately 5% of cases) and *SMC3* (in a single reported case) [Krantz et al., 2004; Musio et al., 2006; Deardorff et al., 2007]. Prevalence is estimated to be as high as 1 in 10,000 [Opitz, 1985], with most cases being sporadic. While several papers have described care of the child with CdLS [Kline et al., 2007] and the natural history of CdLS [Kline et al., 2007], much of what is known about causes of death in these patients stems from a 1985 case series of 48 CdLS patients born between 1917–1982 that included eleven deaths [Beck et al., 1985] and a review by Jackson et al. in 1993 that described 14 deaths [Jackson et al., 1993]. In this study, we present data from the deaths of 426 CdLS patients who died between 1966–2007 and a detailed review of 41 autopsies performed on this cohort from late gestation to 49 years of age. In addition, we review 87 cases of CdLS deaths described in the literature from 1963–2007. These findings will lead to a more profound understanding of the causes of morbidity and mortality in this population, which can be translated into improved care of children and adults with this rare diagnosis by allowing caregivers and physicians to recognize early symptoms and signs and to intervene expediently.

MATERIALS AND METHODS

Under an IRB approved protocol, 426 CdLS cases with a known date of death were selected from our database, of which 295 had a documented cause of death listed (see below). In the 131 deaths for which the COD could not be ascertained, the data was used only in reviewing the average age at death; and not considered in analyzing the causes of death. All probands were previously diagnosed with CdLS by one or more of the authors (LJ, IK, MD, DC, AK, who have considerable experience in diagnosing CdLS) through formal clinical evaluation or direct contact with the family and review of clinical records and photographs. Blood samples were available for 17 of these probands, and *NIPBL* mutations were identified in 15.

Causes of death were determined from review of death certificates, clinical records (including surgical and imaging), autopsy reports, and contact with the family in 295 cases. In those individuals with an identifiable autopsy report (41 cases), the hospital records surrounding the time of death and post mortem examinations were available (38 cases) through contact with the individual families in collaboration with the staff of the CdLS Foundation. Of those individuals with an autopsy report, four were terminated fetuses (ranging from 20 to 23 weeks gestation) with minimal findings (diagnoses confirmed by imaging and in three cases were from families with other CdLS children and confirmed germ line mosaicism in a parent). The complete autopsy reports were reviewed by an independent pathologist (LE). Nineteen further autopsies provided only the cause of death; 45 additional causes of death could be determined either by detailed surgical records just prior to death, imaging of lethal malformations, or detailed clinical records of the terminal illness. Thus 105 of the 295 probands had detailed objective validation of their COD.

Causes of death were assigned to the following primary categories according to major organ system affected: 1) respiratory, which included all primary respiratory infections, including those related to reflux/aspiration, pulmonary embolus (PE), and asthma; 2) gastrointestinal (GI), including primary GI infections, obstruction/volvulus (GIVO), and deaths related to surgical correction of GI problems; 3) cardiovascular (CV), sub-classified into congenital heart disease (CHD), which includes complications from surgical repairs, and other cardiovascular (CV) disease; 4) neurologic (CNS), including seizures and central apnea; 5) accidents; 6) sepsis, including infections without identifiable primary source; 7) renal; 8) cancer; 9) congenital diaphragmatic hernia (CDH); and 10) other.

Cases reported in the literature were identified using Pub Med searches with keywords “Cornelia de Lange Syndrome,” “Brachmann de Lange Syndrome,” “de Lange Syndrome,” “Amsterdam dwarfism,” and analyzing for the COD. Historical cases from prior to the 1970s were identified by following citations from early review articles. Forty-five English language journal articles reporting 87 deaths in CdLS patients were identified in the years 1965–2007. Only in instances where we were sure a particular finding was evaluated on the whole cohort are percentages given; in most cases the raw number of reported cases for an individual finding is stated without a percentage as the denominator is unknown (e.g. unclear if the whole cohort was examined for that particular finding).

RESULTS

Causes of death by age groups

Data were divided by age at time of death into neonatal (deaths in the first 28 days); postnatal (29 days to 1 year); child (>1 and <18 years); and adult (≥ 18 years). Distinct differences in COD in different age groups were noted, and are summarized in Table I and Figures 1 and 2.

Thirty neonates under 28 days of age were included in the Perinatal data set, for which the most common COD was CDH, accounting for more than one third of deaths. CHD caused 5/33 (17%) deaths, and respiratory accounted for 4/30 (13%). Several fetuses with ultrasound-imaged anomalies were terminated and included under “other” causes.

Fifty-one infants from 29 days to 1 year were included in the Postnatal data set. In the postnatal period, the most common causes of death were respiratory 18/51 (35%), CV 14/51 (27%), and GI 9/51 (18%), followed by sepsis 2/51 (4%) and CNS 2/51 (4%). Respiratory deaths in this group were associated with reflux/aspiration in eight cases, pneumonia in four cases and other respiratory causes (including pulmonary edema, apnea, collapsed airway, and pertussis) in five cases. Six of the GI deaths were related to GIVO. An accidental death in this age group was related to a feeding tube incident. The CNS deaths were due to seizures. The CV deaths in this age group were all related to complications of CHD. Other deaths in this age group included complications from prematurity, epidermolysis bullosa, blood clot, and dehydration leading to renal failure.

One hundred and seventeen children >1 and <18 years were included in the Children data set. During childhood, the four most common causes of death were respiratory 38/117 (32%), GI 22/117 (18.8%), accidents, and CV, the latter two accounting for 12/117 (10.2%). Other causes of death included CNS 11/117 (9%), followed by sepsis 7/117 (6%), and renal 3/117 (2.5%). There was one incident of cancer-related death (lymphoma) in this age group. Respiratory deaths were related to reflux/aspiration in 12 cases, bacterial pneumonia in eight cases, viral infection in six cases (including three cases of influenza and two cases of respiratory syncytial virus), and non-specified respiratory causes in 12 cases. GI causes were overwhelmingly related to GIVO (20/22). Two additional GI cases were attributed to

esophagitis/gastritis, and postoperative complications from reflux surgery. Two of the accidental deaths were GI related due to intestinal perforation from feeding tube accidents. CNS causes were attributed to seizures in eight cases and other CNS causes in three cases (including hemorrhage, peri-operative brainstem herniation and shunt infection). In contrast to the infants and neonates, only nine CV deaths were related to CHD and three to non-congenital disease, including congestive heart failure (CHF) in two cases and arrhythmia in one case. Accidents accounted for a much larger percentage of deaths in this group, and included two drownings, two house fires, one fall, one major head trauma, and one institutional death related to rhabdomyolysis after use of restraints.

For 97 propiiti who survived to adulthood, the most common causes of death were respiratory in 31/97 (32%), GI in 25/97 (26%), CNS in 10/97 (10%), accidents in 9/97 (9%), CV in 7/97 (7%), sepsis in 4/97 (4%), and renal in 1/97. There were five cancer deaths in this group, four of which were gastrointestinal (3 esophageal, one gastric), and one unspecified. Of the respiratory causes, 16 deaths were related to reflux/aspiration, 10 to bacterial pneumonia, and five to unspecified respiratory causes. Of the GI deaths, 22 were attributed to GIVO, and one each to pancreatitis, Crohn Disease, and intestinal perforation from a dislodged feeding tube (mechanism not stated/unclear). Deaths related to CNS events were accounted for by seizures in four cases, subdural hemorrhage in two cases, stroke in two cases, and one case each of meningitis and trauma. Two of the CV deaths were related to congenital anomalies, and five others to pericarditis, CHF, myocardial infarction (MI), and cardiomyopathy. Accidental deaths in this age group included one episode of scalding during a bath, a dislodged feeding tube, and a fall. Other deaths in this age group included severe anemia, and two deaths related to respiratory compromise from scoliosis.

Selected Instructional Cases

Detailed autopsy information for of the following cases is included in Table II, with the exceptions of cases 12 and 16, for which such information was not available.

Pneumonia presenting as seizure

Case 1: This female propiiti with a known seizure disorder presented with a fatal seizure at age 2 years 8 months. Post-mortem exam noted a significant neutrophilic infiltrate in the lungs, indicating acute pneumonia. As the blood levels of anti-seizure medication were within therapeutic range at the time of her death, her fatal seizure was thought to be triggered by decreased brain oxygenation caused by the pneumonia.

Intestinal obstruction with minor symptoms

Case 2: A severely-affected 18-year-old male was noted to be weaker and fussy during his feeding and to have some brown material from his G-tube one day before he expired from an undetected small bowel obstruction. When he was admitted to the hospital, he was in renal failure with necrotizing enterocolitis of the cecum and bowel obstruction. Surgical intervention was not attempted.

Case 3: Another female propiiti presented with fever and diarrhea at nine months of age, and was diagnosed with gastroenteritis. Two days later, she presented to the emergency room in shock and with severe acidosis. She was intubated and resuscitated. During this time, she was believed to have a normal abdominal exam and obstruction was not considered as a cause of her acute illness. Several hours following her transfer to intensive care she developed abdominal distension and bilious NG output.

Intestinal obstruction presenting as respiratory distress (131)

Case 4: A severely-affected 8-year-old female presented initially with respiratory symptoms and poor oxygen saturation, but was subsequently found to have intestinal obstruction. It was felt that her respiratory embarrassment may have been caused by increased intra-abdominal pressure related to her intestinal perforation. On autopsy, an underlying malrotation was identified.

Bowel perforation caused by pica

Case 5: This female proposita with a known history of pica died at age 23 from a bowel perforation. Her autopsy revealed aluminum foil and strips of fabric in her small bowel.

Intestinal volvulus caused by surgical adhesions

Case 6: This 13-year-old male presented with acute abdomen and was found to have volvulus related to intra-abdominal adhesions likely caused by prior reflux surgery.

Case 7: In a similar case, a 49-year-old male complained only of constipation before he was found unconscious with bowel obstruction caused by surgical adhesions.

GI hemorrhage from esophagitis and gastritis

Case 8: A 17-year-old male died from GI hemorrhage. Autopsy found extensive erosive gastritis and esophagitis and intestinal metaplasia, alongside myeloid metaplasia possibly indicative of a myeloproliferative disorder.

Gastric herniation

Case 9: This 39-year-old male was “acting normally” per caregivers earlier on the day he died. He was found after expiration and autopsy showed gastric herniation through the diaphragm leading to gastric volvulus.

Necrotizing enterocolitis in a premature infant with malrotation

Case 10: This 5-month-old female infant was delivered at 32 weeks, and had a history of pulmonic stenosis treated with balloon dilatation before she expired from a long course of necrotizing enterocolitis. Autopsy showed malrotation of the GI tract with a foreshortened mesenteric root and volvulus as well as acute on chronic bronchopneumonia with *S. aureus*, both contributing to her demise.

Post-operative death from volvulus surgery

Case 11: This 17-year-old male presented with acute abdomen and was found to have volvulus with necrotic bowel, but died post-operatively. Autopsy found severe GI and abdominal hemorrhage likely caused by post-operative sepsis.

Case 12: Similarly, a 2-year-old female presented with vomiting, abdominal tenderness, and lethargy and expired following surgery for midgut volvulus due to non-fixation of the cecum and ischemic bowel.

Cerebral vascular dissection and infection

Case 13: This female proposita was admitted to the hospital at age 29 with a fever, lethargy and anorexia. She was treated with antibiotics for pneumonia and meningitis without improvement. Post-mortem examination did reveal bronchopneumonia and meningoencephalitis; however, it also revealed a vasculopathy with dissection in the right anterior communicating artery (histological exam showed a ruptured wall with fibrinoid

necrosis and evidence of acute and chronic inflammation suggestive of a focal vasculopathy).

Sudden death attributed to seizure

Case 14: This mildly affected 7-year-old female presented with her first seizure at age seven, and was seen in the emergency department and discharged home. The next evening, her caregivers found her facedown in the bathtub. Post-mortem exam found no evidence of drowning and no etiology for her seizures, and her death was attributed to a seizure and central hypoventilation.

Case 15: Another female proposita died at age 32 when she arrested after a seizure. She was resuscitated but never regained consciousness.

Untreated CHD in an adult

Case 16: This 30-year-old male had a known, unevaluated heart murmur identified on physical exam during childhood. At age 30, he presented in heart failure. Work-up revealed left ventricular failure related to coarctation of the aorta, which had not been previously identified. Surgical intervention was not attempted and he expired.

Unexpected arrhythmia

Case 17: This female proposita presented at age 34 with lethargy and dehydration, and was treated for fungal sepsis and had a gastrostomy tube placed. She was fully improved and was awaiting discharge when she expired. Autopsy findings were consistent with cardiac arrhythmia and heart failure of unknown etiology.

Case 18: This 22-year-old male was recovering uneventfully from aortic valve replacement when he suffered several episodes of aspiration, was re-intubated, and expired from ventricular tachycardia. His death was thought to be related to the stress of aspiration pneumonia on the healing myocardium.

Cardiomyopathy

Case 19: This female proposita with a known right ventricular cardiomyopathy had a fatal arrhythmia at age 36. Her autopsy showed transmural replacement of the right ventricle with adipose tissue.

Self-injurious behavior leading to head trauma

Case 20: This severely-affected 34-year-old female began to have non-seizure drop attacks where she would throw her body to the ground several months prior to her death. The self-injurious behavior was thought to be related to underlying pain or discomfort. However, she suffered fatal traumatic brain injury before an underlying cause could be determined.

Choking, institutional accident

Case 21: This institutionalized 20-year-old male maintained on a soft diet was found unconscious. Medical examination and autopsy revealed an upper airway packed with chunks of solid food and aspirated vomitus in the tracheo-bronchial tree.

Changes in Causes of Death over Time

To evaluate changing awareness and management over the past 41 years, causes of death were evaluated by the year of death. Here, a pattern emerged that demonstrated a decreasing contribution of respiratory causes and increasing contribution of GI causes to deaths (Fig 3). Other causes of death stayed relatively stable over the study period.

Average Age at Death

The average age of death for those in our cohort who survived the neonatal period was 12 years 9 months (N=338); for those who survived past age one year it was 16 years 2 months (N=264); and for those who survived past age 18 it was 28 years 2 months (N=110). As our cohort included only probands who were deceased, these numbers should be interpreted only as data representing the age at death, and not life expectancy of children with CdLS. Figure 4 is a survival curve for our cohort.

Review of Published Cases of CdLS Deaths

In the CdLS literature, there are three case series reporting causes of death in a subset of CdLS study probands. Additionally, there are eighty-seven (87) cases describing the death of a person with CdLS which were identified in the literature from 1963–2007. The causes of death for all these published reports are summarized in Table I.

Autopsy Results

Autopsy findings by organ system are shown in Table II.

Causes of death in the sub-group of cases with detailed clinical records, which included autopsied patients, reflected some differences from the total population incidences (see Table I). In the fetal/early infant cohort who had autopsies and imaging studies, there were more congenital diaphragmatic hernias represented. The intestinal obstruction sequence is also overrepresented due to the surgical cases. Other than the inclusion of more fetal/infant cases, the age range in this group was reflective of the overall distribution of the various CODs. Autopsies with complete organ examination were performed on 38 fetuses and cases from infancy to age 49 years. These offered an opportunity to observe any unusual pattern of structural or physiologic changes. In this report we focus on structural, embryologic, or unexpected histopathologic findings in these 38 complete examinations.

Most of the autopsy findings correlated with the known clinical condition of the individual. Congenital cardiac changes occurred at the expected rate. Gastrointestinal malrotation generally correlated with the terminal episodes of obstruction and presumed volvulus but incidental malrotation was also identified in two instances (one was identified in a stillborn case). Significant autopsy findings (some of which are incidental to the cause of death) by organ system are described below (the actual causes of death are listed at the top of Table II).

Neurologic

Neurologic findings were reported in 20 autopsies. These findings ranged from small brain/microcephaly (15) with convolution abnormalities (2) to complex structural anomalies, including agenesis of the corpus callosum (2), optic nerve hypoplasia (2), frontal lobe shortening (2), and malformation of the inferior olive (2). Some findings provided pathologic evidence for the clinically suspected COD, such as meningoencephalitis with findings of intraventricular, thalamic, subarachnoid, and intraparenchymal hemorrhage; brain swelling leading to herniation; and cortical infarction with subdural hemorrhage and neuronal necrosis. Other findings related to old injury or disease processes including evidence of old contusions, hemorrhage, and edema.

Cardiovascular

Autopsy confirmed congenital anomalies in 14 cases, consistent with premortem findings from the literature [Jackson 1993]. The most commonly reported were patent foramen ovale (PFO) (5), bicuspid aortic valve (2), pulmonic valve abnormalities (2), coronary artery

abnormalities (2), aberrant subclavian artery (1), ventricular septal defect (VSD) (1), atrial septal defect (ASD) (1), tetralogy of Fallot (TOF) (1), and common atrioventricular canal (CAVC) (1). Other CV findings revealed acquired disease processes, such as left ventricular hypertrophy (LVH) (3), right ventricular hypertrophy (RVH) (1), cardiac dilatation (2), cardiomyopathy with arrhythmogenic RV dystrophy (1), and pericardial effusion (1).

Pulmonary

In addition to infiltrates and effusions noted on all patients who suffered from pneumonia at the time of death and pulmonary hypoplasia in those with CDH, other pulmonary findings included bronchopulmonary dysplasia and hyaline membrane disease (2), chronic tracheitis (1), acute respiratory distress syndrome (1), pulmonary thromboembolism (1), and granulomas likely related to cytomegalovirus infection (1). Lung lobation and asymmetry abnormalities were also frequent, and were noted in six cases.

Oropharynx and Palate

Cleft soft palate was a common finding, noted in five probands.

Gastrointestinal

The majority of the GI findings related to underlying disease processes causing death, or the effects of chronic reflux. Three probands had reflux esophagitis or gastritis, one with marked hyperplasia and petechiae related to a gastrostomy tube. The proband who died from an upper GI bleed (Case 8) had severe hemorrhagic gastritis and esophagitis, chronic gastritis, intestinal metaplasia, and transmural fibrosis of the esophagus. The proband in Case 21, who died from choking, had an esophagus packed with food. The proband in Case 2, who died from intestinal obstruction, had necrotizing enterocolitis of the cecum with pseudomembranes. Three probands who died from volvulus/obstruction had underlying malrotation, and two had evidence of surgical adhesions leading to volvulus.

Congenital abnormalities of the bowel were frequent with small bowel duplication in one proband and malrotation in nine probands (including two with undiagnosed malrotation that died from non-GI causes).

Liver findings were generally nonspecific and included congestion and hepatocellular necrosis likely related to underlying disease processes and shock in six probands. There were also reports of liver atrophy, enlarged left lobe, transfusion-related siderosis, hemangioma, and an atretic gall bladder.

Genitourinary

Genitourinary findings are a common occurrence in CdLS. Renal anomalies included small kidneys in three probands, horseshoe kidneys in four probands, and reports of atrophy, thyroidization, glomerulosclerosis, cortical cysts and interstitial nephritis.

Genital abnormalities included seven reports of bicornate uterus and three reports of ovarian atrophy in girls. Hypospadias and micropenis were recorded in five cases, cryptorchidism in four, and small testes in two of the 12 reports from males.

Splenopancreatic fusion

This unusual finding was noted in nine cases and was usually described as an accessory spleen found within the tail of the pancreas, with mingling of splenopancreatic tissue that was histologically indistinguishable from each other. In addition, there were two cases of

accessory spleens not related to the pancreas, and one finding of splenomegaly in a propositus with possible myeloproliferative disorder.

Endocrine

Multiple autopsies recorded endocrine abnormalities, notably adrenal atrophy and hypoplasia (4), fused/contiguous adrenal glands (1), adrenal hemorrhage (1), hypercellular parathyroid (1), ectopic parathyroid (1-located in pharynx), adenohypophyseal cyst (1), and Hashimoto's thyroiditis (1).

Immunologic

Multiple autopsies (11) recorded abnormalities of the thymus, notably premature involution (6), enlarged Hassall's corpuscles (1), thymic dysplasia (1), cortical depletion (1), and complete absence of the thymus (1).

Pathologic findings in the literature

Pathologic findings from the literature are summarized in Table II.

Fifty-one autopsies are reported in the CdLS literature [Ptacek et al., 1963; Schlesinger et al., 1963; Thornburn 1964; Bjorklof et al., 1965; Choo et al., 1965; Falek et al., 1965; Gans et al., 1965; Hart et al., 1965; Huang et al., 1967; McArthur et al., 1967; France et al., 1969; Berg et al., 1970; Lacourt et al., 1977; Taylor et al., 1981; Wick et al., 1982; Westergaard et al., 1983; Beck et al., 1985; Sato et al., 1986; Maruiwa et al., 1988; Filippi 1989; Heckmann et al., 1991; Jelsema et al., 1993; Pankau et al., 1993; Veall 1994; DuVall et al., 1996; Hayashi et al., 1996; Manouvrier et al., 1996; Boog et al., 1999; Yamaguchi et al., 1999; Fernandez et al., 2000; Ohkusu et al., 2001; Vuilleumier et al., 2002; Arbuzova et al., 2003; Hulinsky et al., 2005; Price et al., 2005]. Cardiac abnormalities were quite common, noted in 29 of the autopsies, and included 19 cases involving congenital heart defects. Pulmonary findings generally included abnormalities related to death, such as pneumonia and CDH, but also included findings of abnormal lung lobation. Given the large number of deaths related to GIVO, GI anomalies reported in the literature were carefully reviewed for underlying anatomic abnormalities that could lead to this presentation. Indeed, although only one death in the literature was directly related to volvulus/obstruction, there were 11 cases of intestinal rotation and mesenteric fixation abnormalities reported. Other GI findings included cysts throughout the GI tract, colonic duplication, duodenal atresia, pyloric stenosis, fatty liver, hepatic congestion and hemangioendotheliomas [Maruiwa et al., 1988]. Genitourinary findings included ovarian/testicular hypoplasia (8) and other abnormalities, including small/underdeveloped kidneys. There was also one Wilms tumor found on examination of a child who died from bronchopneumonia [Maruiwa et al., 1988]. Endocrine abnormalities were also common, noted in 9 cases, including adrenal, thyroid, and parathyroid changes.

DISCUSSION

As with many rare genetic disorders, the ability to identify large numbers of affected propoiti is limited. Working with the support of the CdLS Foundation (<http://www.cdlsusa.org/>), a parent and family support group, we have tried to identify as many reported causes of death and documented autopsies as possible in individuals with CdLS to better understand contributors to morbidity and mortality in this diagnosis that may allow improved anticipatory management. This work represents a cohort of twenty times any previously reported series of causes of death and autopsy findings in CdLS. Even so, the small numbers have poor statistical power and this report focuses mainly on observed trends.

We clearly have several sources of bias in our data. 1) We are largely reporting propoiti from North America, which traditionally has lower infant mortality than other continents, partly due to a lower threshold for intervention for children with severe genetic syndromes. 2) Our death rates are probably lower than actual rates secondary to decreased reporting of death to us as non-primary care clinicians by families. This underreporting may also bias those reported to more “dramatic” causes of death, and perhaps there may be an increased incidence of pneumonia, asthma, and seizure deaths that we have not appreciated.

The most surprising finding from this data is the percentage of deaths attributable to GIVO. In addition to the deaths described above, multiple case reports of non-fatal GIVO successfully treated with colonic resection also exist [Husain et al., 1994; Masumoto et al., 2001; Takada et al., 2007]. As surgical techniques have improved, so has survival. However, survival depends on timely recognition and intervention. Many of the cases in our population were unsuspected clinically until late in the evolution of the terminal episode. This is not only due in part to the non-verbal development of many individuals with CdLS, but also to the lack of a clear symptom picture pointing at the intestinal problem. A quote from one autopsy illustrates this:

“23 yr old girl small and fairly typical for CdLS with marked microcephaly. Seen at 1430 hrs (date) with vomiting and not drinking fluids. No remark about complaint or demonstration of pain. WBC 30,000, no temperature noted. Given prescription for antibiotic. Later found at the group home with absent vital signs. Autopsy done about 24hrs later. At autopsy the colon was abnormal in that it was completely mobile and not adherent to the retroperitoneal space with mobility from the rectum to the ileocecal valve. The colon, from about mid-sigmoid all the way to the ileocecal valve, had twisted (volvulus) resulting in vascular obstruction and portions of the colon appeared necrotic. The colon was massively distended and filled with intestinal fluid admixed with blood. The small bowel was also distended but did not appear to be involved with the volvulus.”

This report highlights the discrepancy between the pathological findings and the clinical symptoms and presentation in the setting of bowel obstruction and volvulus in CdLS. The girl really had only vomiting as a symptom and little else. Given her non-specific symptoms of vomiting and poor oral intake, she was not recognized as ill enough for treatment or surgical intervention until she was irreversibly compromised. Unfortunately this sequence is not unusual in the experience reported here.

Interestingly, the number of deaths in our population that were related to GIVO (49) is slightly over twice the number reported in the literature (22). This may, in part, represent failure to appreciate gastrointestinal obstruction as a COD until recently, and is supported by the finding of intestinal rotation abnormalities as incidental findings on post-mortem examination in 11 published cases. In addition, most deaths of GIVO occur in the school-age years, suggesting that increased survival of children with CdLS has allowed them to survive to an age when GIVO is more common. While underlying malrotation of the intestine is certainly a predisposing factor for volvulus and obstruction, children with CdLS have several other predisposing factors for GI obstruction. In their report on 15 children with mental disability (six with CdLS), Takada et al., (2007) suggest that in addition to underlying malrotation, adhesions from abdominal surgery (many individuals with CdLS have undergone Nissen funduplications for correction of severe reflux), aerophagia, constipation, pica, and difficulty in verbal communication, all contribute to the risk of morbidity and mortality from GI obstruction. GIVO as a significant contributor to overall causes of death in the CdLS patient underscores the importance of timely recognition and evaluation for obstruction in the patient with any change in behavior, mental status, or GI symptoms.

The impact of reflux is also seen in the incidence of reflux-related cancers, with esophageal cancer listed as the COD in three cases and stomach cancer in one case among those in our study who survived to adulthood. Our data underscores a need for aggressive management of reflux, which has been shown to be present in close to 100% of individuals with CdLS. Timely intervention in all cases of respiratory infection with organism identification and treatment with appropriate antibiotics is also critical.

The discrepancy in the number of deaths attributable to CDH seen in our cohort compared to the literature is likely due to the cohort size. While both our cohort and the literature saw comparable numbers of CDH-related deaths in the neonatal period (15 and 18, respectively), the total number of individuals clearly was almost three times that of reported cases. Both our cohort and the literature review identified similar number of neonates (30 and 41, respectively), in whom CDH-related death is seen.

The majority of our study patients died from respiratory causes. In contrast to clinically unsuspected GI deaths, most respiratory infections were evident prior to death, and patients generally presented with fever and typical respiratory symptoms. While many of these events can be attributed to the severe (and often unrecognized) reflux and aspiration associated with CdLS, it remains that CdLS patients seem more susceptible to life-threatening respiratory infections. Indeed, many reports in the literature suggest that CdLS patients are more susceptible to infection that is often resistant to antibiotics. To date, no underlying immunologic abnormality is known in CdLS patients, however, thymic anomalies were noted on 9/38 of the autopsies conducted on our study population, ranging from mild cortical depletion to complete absence of the thymus. This finding raises the possibility of an underlying immunologic abnormality as a contributing cause, and more research is clearly needed on this subject. In addition, several of the autopsies (5) reported abnormalities in lung lobation and vascularization, raising the possibility that these anatomic abnormalities may lead to an increased susceptibility to infection.

Some of the most unnerving deaths in the cases presented above are those in which an ostensibly healthy, or recovering, child dies suddenly from causes related to apnea/central hypoventilation, such as those in Cases 14, 15, and 18, described above. Two published cases describe episodes of apnea in CdLS patients: the apnea death of a 21-year-old man following a dental procedure [Filippi 1989], and a one-month-old infant who experienced non-fatal respiratory arrest lasting several minutes during an orthodontic impression for cleft palate [Chate et al., 1994]. Another case reports seizures provoked by obstructive apnea in a child with CdLS [Nechay et al., 2006]. This child did not respond to anti-epileptic medications and his seizures stopped with correction of his upper airway obstruction. These cases underscore the importance of pulse oximeter monitoring in the post-operative and recovery phases of even minor procedures.

Children and adults with CdLS seem to be at a slightly higher risk for accidental deaths than their healthy counterparts, with accidents accounting at least in part for 21 deaths in our sample (7.1%), compared to 4.7% of deaths in the general population (2004). Only two accidental deaths were reported in the literature (1%), likely due to decreased reporting for this type of death. An increase in pain tolerance and inability of many CdLS children to verbally express pain and discomfort may lead to accidents involving feeding tubes and bath scalding, especially in institutions where caregivers are often responsible for several patients at a time.

It is important to recognize that many of these deaths were related to peri-operative complications and to withdrawal of care. At least 9/295 of the deaths in our study group were directly related to withdrawal of supportive technology, although they are listed under

the primary cause of disease (i.e. pneumonia leading to intubation). At least 27/295 of the deaths are related temporally to surgical interventions. Whether these deaths represent true surgical complications (i.e. post-operative pneumonias and infections) or direct mortality from the primary cause (i.e. congenital heart disease and emergency surgery for intestinal perforation) is difficult to determine, but these deaths underscore the importance of timely recognition of medical problems and special medical attention for these patients, as well as the necessity of initiating end of life discussions with the family as appropriate.

Recommendations for age-specific monitoring and care are listed in Table III. These recommendations are extrapolated from the data presented here and delineate approaches to cautious care for the individual with CdLS based on the observed trends. Overall, it seems that a proactive approach to care is warranted in this patient population, given the difficulties in assessment, minimal symptomatology and rapid progression to catastrophic outcome in some patients. Prospective studies will be needed to assess the value of these interventions in the health outcomes for this population but in the meantime seem prudent given the specificity and prevalence of the adverse outcomes and contribution to morbidity and mortality observed in this study.

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References

1. Deaths: Final Data for 2004. C. f. D. Control, Center for Disease Control.
2. Arbuzova S, Nikolenko M, Krantz ID, Hallahan T, Macri J. Low first-trimester pregnancy-associated plasma protein-A and Cornelia de Lange syndrome. *Prenat Diagn.* 2003; 23:864. [PubMed: 14558036]
3. Beck B, Fenger K. Mortality, pathological findings and causes of death in the de Lange syndrome. *Acta Paediatr Scand.* 1985; 74:765–769. [PubMed: 4050424]
4. Berg, JM.; McCreary, BD.; Redler, MAC.; Smith, GF. The de Lange Syndrome. Oxford: Pergamon Press; 1970. p. 31-53.
5. Bjorklof K, Brundelet P. Typus Degenerativus Amstelodamensis (Cornelia de Lange First Syndrome). *Acta Paediatr Scand.* 1965; 54:275.
6. Boog G, Sagot F, Winer N, David A, Nombalais MF. Brachmann-de Lange syndrome: a cause of early symmetric fetal growth delay. *Eur J Obstet Gynecol Reprod Biol.* 1999; 85:173–177. [PubMed: 10584631]
7. Chate RA. Respiratory arrest during an orthodontic impression of a cleft palate, in a baby with Brachmann-de Lange syndrome. *J R Coll Surg Edinb.* 1994; 39:121–123. [PubMed: 7520068]
8. Choo PB, Bianchi GN. Brachmann-De Lange Syndrome: A report of four cases. *Aust Paediatr J.* 1965; 1:236.
9. Deardorff MA, Kaur M, Yaeger D, Rampuria A, Korolev S, Pie J, Gil-Rodriguez C, Aernedo M, Loeys B, Kline AD, Wilson M, Lillquist K, Sui V, Ramos FJ, Musio A, Jackson LS, Dorsett D, Krantz ID. Mutations in cohesin complex members SMC3 and SMC1A cause a mild variant of cornelia de Lange syndrome with predominant mental retardation. *Am J Hum Genet.* 2007; 80:485–494. [PubMed: 17273969]
10. DuVall GA, Walden DT. Adenocarcinoma of the esophagus complicating Cornelia de Lange syndrome. *J Clin Gastroenterol.* 1996; 22:131–133. [PubMed: 8742653]
11. Falek A, Schmidt R, Jarvis GA. Brachman-De Lange Syndrome. *Lancet.* 1965; 1:706–707. [PubMed: 14258562]

12. Fernandez HH, Friedman JH, Famiglietti EV. Probable Cornelia de Lange syndrome with progressive parkinsonism and dystonia. *Mov Disord.* 2000; 15:749–751. [PubMed: 10928594]
13. Filippi G. The de Lange syndrome. Report of 15 cases. *Clin Genet.* 1989; 35:343–363. [PubMed: 2758687]
14. France NE, Crome L, Abraham JM. Pathological features in the de Lange syndrome. *Acta Paediatr Scand.* 1969; 58:470–480. [PubMed: 5365170]
15. Gans B, Thurston JG. De Lange's Amsterdam Dwarfs Syndrome. Report of four cases. *Dev Med Child Neurol.* 1965; 38:42–45. [PubMed: 14292515]
16. Hart ZH, Jaslow RI, Gomez MR. The De Lange Syndrome. *Am J Dis Child.* 1965; 109:325–332. [PubMed: 14261013]
17. Hayashi MK, Sakamoto K, Kurata K, Nagata J, Satoh J, Morimatsu Y. Septo-optic dysplasia with cerebellar hypoplasia in Cornelia de Lange syndrome. *Acta Neuropathol (Berl).* 1996; 92:625–630. [PubMed: 8960322]
18. Heckmann H, Ang LC, Casey R, George DH, Lowry N, Shokeir MH. Leigh's disease with clinical manifestations of Cornelia de Lange syndrome. *Pediatr Neurosurg.* 1991; 17:192–195. [PubMed: 1822133]
19. Huang CC, Emanuel I, Huang SW, Chen TY. Two cases of the de Lange syndrome in Chinese infants. *J Pediatr.* 1967; 71:251–254. [PubMed: 6029474]
20. Hulinsky R, Byrne JL, Lowichik A, Viskochil DH. Fetus with interstitial del(5)(p13.1p14.2) diagnosed postnatally with Cornelia de Lange syndrome. *Am J Med Genet A.* 2005; 137:336–338. [PubMed: 16086407]
21. Husain K, Fitzgerald P, Lau G. Cecal volvulus in the Cornelia de Lange syndrome. *J Pediatr Surg.* 1994; 29:1245–1247. [PubMed: 7807358]
22. Jackson L, Kline AD, Barr MA, Koch S. de Lange syndrome: a clinical review of 310 individuals. *Am J Med Genet.* 1993; 47:940–946. [PubMed: 8291537]
23. Jelsema RD, Isada NB, Kazzi NJ, Sargent K, Harrison MR, Johnson MP, Evans MI. Prenatal diagnosis of congenital diaphragmatic hernia not amenable to prenatal or neonatal repair: Brachmann-de Lange syndrome. *Am J Med Genet.* 1993; 47:1022–1023. [PubMed: 8291516]
24. Kline AD, Grados M, Sponseller P, Levy HP, Blagowidow N, Schoedel C, Rampolla J, Clemens DK, Krantz I, Kimball A, Pichard C, Tuchman D. Natural history of aging in Cornelia de Lange syndrome. *Am J Med Genet C Semin Med Genet.* 2007; 145:248–260. [PubMed: 17640042]
25. Kline AD, Krantz ID, Sommer A, Kliewer M, Jackson LG, FitzPatrick DR, Levin AV, Selicorni A. Cornelia de Lange syndrome: clinical review, diagnostic and scoring systems, and anticipatory guidance. *Am J Med Genet A.* 2007; 143:1287–1296. [PubMed: 17508425]
26. Krantz ID, McCallum J, DeScipio C, Kaur M, Gillis LA, Yaeger D, Jukofsky L, Wasserman N, Bottani A, Morris CA, Nowaczyk MJ, Toriello H, Bamshad MJ, Carey JC, Rappaport E, Kawauchi S, Lander AD, Calof AL, Li HH, Devoto M, Jackson LG. Cornelia de Lange syndrome is caused by mutations in NIPBL, the human homolog of *Drosophila melanogaster* Nipped-B. *Nat Genet.* 2004; 36:631–635. [PubMed: 15146186]
27. Lacourt GC, Arendt J, Cox J, Beguin F. Microcephalic dwarfism with associated low amniotic fluid 5-hydroxyindole-3-acetic acid (5HIAA). Report of a case of Cornelia de Lange syndrome. *Helv Paediatr Acta.* 1977; 32:149–154. [PubMed: 617972]
28. Manouvrier SM, Espinasse M, Vaast P, Boute O, Farre I, Dupont F, Puech F, Gosselin B, Farriaux JP. Brachmann-de Lange syndrome: pre- and postnatal findings. *Am J Med Genet.* 1996; 62:268–273. [PubMed: 8882785]
29. Maruiwa M, Nakamura Y, Motomura K, Murakami T, Kojiro M, Kato M, Morimatsu M, Fukuda S, Hashimoto T. Cornelia de Lange syndrome associated with Wilms' tumour and infantile haemangioendothelioma of the liver: report of two autopsy cases. *Virchows Arch A Pathol Anat Histopathol.* 1988; 413:463–468. [PubMed: 2845644]
30. Masumoto K, Izaki T, Arima T. Cornelia de Lange syndrome associated with cecal volvulus: report of a case. *Acta Paediatr.* 2001; 90:701–703. [PubMed: 11440107]
31. McArthur RG, Edwards JH. De Lange syndrome: report of 20 cases. *Can Med Assoc J.* 1967; 96:1185–1198. [PubMed: 6022788]

32. Musio A, Selicorni A, Focarelli ML, Gervasini C, Milani D, Russo S, Vezzoni P, Larizza L. X-linked Cornelia de Lange syndrome owing to SMC1L1 mutations. *Nat Genet.* 2006; 38:528–530. [PubMed: 16604071]
33. Nechay A, Smulska N, Chepiga L. Anoxic-epileptic seizures in Cornelia de Lange syndrome: case report of epileptic seizures induced by obstructive apnea. *Eur J Paediatr Neurol.* 2006; 10:142–144. [PubMed: 16713315]
34. Ohkusu K, Nakamura A, Horie H, Udagaw A. Fatal sepsis associated with acute pancreatitis caused by *Moraxella catarrhalis* in a child. *Pediatr Infect Dis J.* 2001; 20:914–915. [PubMed: 11734777]
35. Opitz JM. The Brachmann-de Lange syndrome. *Am J Med Genet.* 1985; 22:89–102. [PubMed: 3901753]
36. Pankau R, Janig U. Diaphragmatic defect in Brachmann-de Lange syndrome: a further observation. *Am J Med Genet.* 1993; 47:1024–1025. [PubMed: 8291517]
37. Price N, Bahra M, Griffin D, Hanna G, Stock A. Cornelia de Lange Syndrome in association with a balanced reciprocal translocation involving chromosomes 3 and 5. *Prenat Diagn.* 2005; 25:602–603. [PubMed: 16032773]
38. Ptacek LJ, Opitz JM, Smith DW, Gerritsen T, Waisman HA. The Cornelia De Lange Syndrome. *J Pediatr.* 1963; 63:1000–1020. [PubMed: 14071035]
39. Sato A, Kajita A, Sugita K, Izumi T, Fukuyama Y, Funata N, Okeda R. Cornelia de Lange syndrome with intracranial germinoma. *Acta Pathol Jpn.* 1986; 36:143–149. [PubMed: 3962671]
40. Schlesinger B, Clayton B, Bodian M, Jones KV. Typus Degenerativus Amstelodamensis. *Arch Dis Child.* 1963; 38:349–357. [PubMed: 14058809]
41. Takada K, Hamada Y, Sato M, Fujii Y, Teraguchi M, Kaneko J, Kamiyama Y. Cecal volvulus in children with mental disability. *Pediatr Surg Int.* 2007
42. Taylor MJ, Josifek K. Multiple congenital anomalies, thymic dysplasia, severe congenital heart disease, and oligosyndactyly with a deletion of the short arm of chromosome 5. *Am J Med Genet.* 1981; 9:5–11. [PubMed: 6264787]
43. Thornburn M. De Lange's syndrome in a newborn Jamaican infant. *Am J Obstet Gynecol.* 1964; 89:828–829. [PubMed: 14198989]
44. Veall GR. An unusual complication of Cornelia de Lange syndrome. *Anaesthesia.* 1994; 49:409–410. [PubMed: 8209982]
45. Vuilleumier NE, Kovari E, Michon A, Hof PR, Mentenopoulos G, Giannakopoulos P, Bouras C. Neuropathological analysis of an adult case of the Cornelia de Lange syndrome. *Acta Neuropathol (Berl).* 2002; 104:327–332. [PubMed: 12172920]
46. Westergaard JG, Chemnitz J, Teisner B, Poulsen HK, Ipsen L, Beck B, Grudzinskas JG. Pregnancy-associated plasma protein A: a possible marker in the classification and prenatal diagnosis of Cornelia de Lange syndrome. *Prenat Diagn.* 1983; 3:225–232. [PubMed: 6194522]
47. Wick MR, Simmons PS, Ludwig J, Kleinberg F. Duodenal obstruction, annular pancreas, and horseshoe kidney in an infant with Cornelia de Lange syndrome. *Minn Med.* 1982; 65:539–541. [PubMed: 7177088]
48. Yamaguchi K, Ishitobi F. Brain dysgenesis in Cornelia de Lange syndrome. *Clin Neuropathol.* 1999; 18:99–105. [PubMed: 10192706]

Figure 1.
Summary representative figure with organ systems affected

Figure 2.
Causes of Death by age in our cohort

Figure 3.
Changes in causes of death over time

Figure 4.
Survival curve

Table I

Summary of causes of death in our cohort and the literature

Cause of Death	CHOP ¹ Cohort		% of CHOP total [*]	% of Lit ² total [*]
Respiratory	<i>Aspiration</i>	12%	31%	30%
	<i>Pneumonia</i>	7%		
	<i>Viral URI</i>	2%		
	<i>Other</i>	9%		
Gastrointestinal	<i>GIVO</i>	16%	19%	13%
	<i>Other</i>	3%		
Neurological	<i>Seizures</i>	4%	8%	7%
	<i>Other</i>	3%		
Cardiovascular	<i>Congenital</i>	10%	13%	15%
	<i>Other</i>	3.5%		
CDH			5%	20%
Accidental			8%	1%
Sepsis			4%	0%
Renal			2%	2%
Cancer			2%	2%
Other			9%	9%
TOTAL			100%	100%

* Calculated out of 295 propositi at CHOP, 87 propositi in the literature.

¹ CHOP – Children’s Hospital of Philadelphia ²Lit – Literature

CASE	1	2	3	4	5	6	7	8	9	10
RES <i>Spleno-pancreatic fusion</i> <i>Other RES</i>		+	+	+	+					+ + siderosis
Endocrine <i>Adrenal hypoplasia/atrophy</i> <i>Other</i>				+			adenohypophyseal cyst		+	Parathyroid dysplasia
Immune										
<i>Thymus hypoplasia/dysplasia</i>		+	+	+		+				
Neuro <i>Microcephaly</i>			+	+	+				+	+
Musculoskeletal <i>Scoliosis</i> <i>sacral dimple/tag</i> <i>Club foot</i> <i>Accessory ribs</i> <i>Other MS</i>	+ + 			+				+		ovoid vertebral bodies

CASE	11	13	14	17	18	19	20	21	22	23
Age/Gender	17/11 M	29/02 F	07/11 F	35/01 F	22/03 M	36/09 F	34/03 F	20/00 M	00/00 F	01/00 F
COD	GI: GIVO	Resp: PNA, PE; CNS: meningitis	CNS: Seizure	CV: arrhythmia	CV: CHD/ARDS	CV: arrhythmia	CNS: SDH, Resp: PNA	Resp: Reflux/Asp	CDH	PNA
CV <i>CHD</i> <i>Acquired</i>			+ Dilatation	+ ASD, Valve anomaly	+ Valve anomaly	+ Dysplasia			+ TOF	
Respiratory <i>Anatomic</i> <i>PNA</i>	+ Trilobe	+					+	+	+ CDH	

CASE	11	13	14	17	18	19	20	21	22	23
Edema/ARDS Other Resp	+	+	+							+ emphysema
GI										
Cleft palate										
Esophagitis/Gastritis	+						+			
Rotation Abnormalities	+									
Other GI									+ adhesions	
Hepatic/Biliary anatomy										
GU										
Horseshoe kidney				+						
Hypoplastic/Dysplastic kidney	+			+ AIN			+			
Other kidney				NA	+		NA		NA	+ cysts
Cryptorchidism				NA		NA				NA
Bicornate Uterus	NA			+	NA		+	NA	+	
Gonadal Hypoplasia								+		
Hypoplastic genitals										
Breast										
Other GU								+ fibrocyst disease		
RES										
Spleno-pancreatic fusion										
Other RES									+ accessory spleens	
Endocrine										
Adrenal hypoplasia/atrophy										
Other				Thyroiditis					fused adrenals	
Immune										
Thymus hypoplasia/dysplasia							+			+
Neuro										
Microcephaly	+	+		+		+		+		+

CASE	11	13	14	17	18	19	20	21	22	23
Musculoskeletal										
<i>Scoliosis</i>										
<i>sacral dimple/tag</i>										
<i>Club foot</i>										
<i>Accessory ribs</i>						+			+	
<i>Other MS</i>						cataract				

CASE	24	25	26	27	28	29	30	31	32	33
Age/Gender	04/03 F	23/02 F	00/00 M	00/00 F	04/08 F	00/00 M	02/05 F	00/00 M	00/00 F	02/08 M
COD	GI: GIVO	CNS: seizures	Fetal	CDH	GI: GIVO	Fetal	Renal: uro-sepsis	Fetal	Other: Prema-turity	Resp: PNA
CV										
<i>CHD</i>	+ VSD						+ CAVC			
<i>Acquired</i>								+ Aberrant Subclavian Artery		
Respiratory										
<i>Anatomic</i>										
<i>PNA</i>	+									
<i>Edema/ARDS</i>	+									
<i>Other Resp</i>										
GI										
<i>Cleft palate</i>				+			+			
<i>Esophagitis/Gastritis</i>										
<i>Rotation Abnormalities</i>	+				+					
<i>Other GI</i>										
<i>Hepatic/Biliary anatomy</i>					+ enlarged					
GU										
<i>Horshoe kidney</i>	+		+							
<i>Hypoplastic/Dysplastic kidney</i>										
<i>Other kidney</i>							+ UTI			
<i>Cryptorchidism</i>	NA	NA		NA	NA		NA	NA		+

CASE	24	25	26	27	28	29	30	31	32	33
<i>Bicornate Uterus</i> <i>Gonadal Hypoplasia</i> <i>Hypoplastic genitals</i> <i>Breast</i> <i>Other GU</i>			NA	+	+	NA	+	NA	+	NA
			+ hypoplastic nipples				+ recto-vaginal fistula	+		
RES										
<i>Spleno-pancreatic fusion</i> <i>Other RES</i>				+		+	+ splenomegaly		+ accessory spleen	reactive lymph nodes
Endocrine										
<i>Adrenal hypoplasia/atrophy</i> <i>Other</i>								+	+ ectopic parathyroid	
Immune										
<i>Thymus hypoplasia/dysplasia</i>							+	+		
Neuro										
<i>Microcephaly</i>	+	+					+	+		
Musculoskeletal										
<i>Scoliosis</i> <i>sacral dimple/tag</i> <i>Club foot</i> <i>Accessory ribs</i> <i>Other MS</i>				+	+	+	+		+	

CASE	34	35	36	37	38	39	40	41	Literature Summary N=51		Minimum Prevalence
Age/Gender	23/05 F	19/11 F	01/06 F	38/01 F	02/04 M	26/03 F	00/00 M	00/00 U			
COD	GI: GIVO	GI	Renal: urosepsis	Resp: PNA	Resp: PNA	Resp: Reflux/Asp	Resp: Prematurity	Fetal			
CV											
<i>CHD</i> <i>Acquired</i>					+ PFO + LVH, dilated RV	+ PFO	+ Valve anomaly		29		43/89

CASE	34	35	36	37	38	39	40	41	Literature Summary N=51	Minimum Prevalence
Respiratory										
<i>Anatomic</i>									lobation (5), CDH (5)	lobation, 11/89; CDH 9/89
<i>PNA</i>		+				+			17	26/89
<i>Edema/ARDS</i>	+								5	12/89
<i>Other Resp</i>				+ adhesions			+ HMD		hemorrhage (3), emphysema (1)	
GI										
<i>Cleft palate</i>							+		8	14/89
<i>Esophagitis/Gastritis</i>									3	8/89
<i>Rotation Abnormalities</i>	+		+		hiatal hernia; +Meckel's; pyloric stenosis	+	+ small bowel duplication		11	20/89
<i>Other GI</i>		perforated duodenum	+ adhesions						pyloric stenosis (2), esophageal stenosis (1), esophageal diverticulum (1), annular pancreas (2), pyloric atresia (1), multiple colonic polyps (1), colonic duplication (1), duodenal atresia (1)	
<i>Hepatic/Biliary anatomy</i>									abnormal lobation (1)	
GU										
<i>Horseshoe kidney</i>									4	8/89
<i>Hypoplastic/Dysplastic kidney</i>									5	8/89
<i>Other kidney</i>				chronic inflammation	+ fetal lobulation				cysts (5)	
<i>Cryptorchidism</i>	NA	NA	NA	NA	+	NA			10	16/89
<i>Bicornate Uterus</i>				+	NA		NA		6	13/89
<i>Gonadal Hypoplasia</i>				+		+			8	15/89
<i>Hypoplastic genitals</i>					+		+		1	8/89
<i>Breast</i>									hypoplastic nipples (1)	hypoplastic nipples 7/89
<i>Other GU</i>										
RES										
<i>Spleno-pancreatic fusion</i>						+	+		7	16/89
<i>Other RES</i>										
Endocrine										
<i>Adrenal hypoplasia/atrophy</i>									9	13/89
<i>Other</i>									thyroid vacuolization/hypoplasia (9), fused adrenals (4), pituitary hypoplasia (3)	

CASE	34	35	36	37	38	39	40	41	Literature Summary N=51	Minimum Prevalence
Immune										
Thymus hypoplasia/dysplasia	+								hypoplasia/atrophy (9), absence of Hassal' s corpuscles (1), prominent, distended Hassal bodies (2), lymphocyte depletion (1)	22/89
Neuro Microcephaly	+	+				+			15	33/89
Musculoskeletal Scoliosis sacral dimple/tag Club foot Accessory ribs Other MS						+			1 1 immature cartilage (2), cataracts (2)	4/89 5/89

*) (+) indicated presence of feature; no notation indicates feature not noted; NA = not applicable; M = male; F= female; U = unknown gender; 00/00 = age denoted in years/months; AIN = acute interstitial necrosis; ARDS = Acute respiratory distress syndrome; ASD = atrial septal defect; Asp = aspiration; BPD = broncho-pulmonary dysplasia; CAVC = CDH = congenital diaphragmatic hernia; CHD = congenital heart disease; COD = cause of death; CNS = central nervous system; CV = cardiovascular; GE = gastroesophageal; GI = gastrointestinal; GfVO = gastrointestinal/volvulus/obstruction; GS = glomerular sclerosis; GU = genito-urinary; HMD = hyaline membrane disease; LVH = left ventricular hypertrophy; MS = musculoskeletal; NEC = necrotizing enterocolitis; Neuro = neurologic; PE = pulmonary embolus; PFO = patent foramen ovale; PNA = pneumonia; PS = pulmonic stenosis; RES = reticul-endothelial system; Resp = respiratory; RV = right ventricle; RVH = right ventricular hypertrophy; SDH = subdural hemorrhage; TOF = tetralogy of Fallot; UTI = urinary tract system; VSD = ventricular septal defect.

Table III

Recommendations for age-specific management and surveillance of CdLS individuals

Problem	Newborn/Infant Management	Child/Adult Management
Gastroesophageal Reflux	Aggressive medical and surgical management of reflux	Aggressive medical and surgical management of reflux
	Careful monitoring for aspiration pneumonia.	Careful monitoring for aspiration pneumonia
	Consider apnea monitor/sleep study in those at high risk	Routine evaluation for esophageal pathology and reflux complications such as ongoing reflux, stricture, esophageal corrosion, Barrett’s esophagus
GI Volvulus/Obstruction	Malrotation evaluation and correction if warranted	Malrotation evaluation and correction
	Evaluate for adhesions and other related causes of obstruction	Evaluate for adhesions and other related causes of obstruction
	Consider volvulus/obstruction in any individuals with <div><div>1</div><div>Change in mental status</div></div> <div><div>2</div><div>Abdominal distention</div></div> <div><div>3</div><div>Emesis</div></div> <div><div>4</div><div>Self-injurious behavior</div></div>	Consider volvulus/obstruction in any individuals with <div><div>1</div><div>Change in mental status</div></div> <div><div>2</div><div>Abdominal distention</div></div> <div><div>3</div><div>Emesis</div></div> <div><div>4</div><div>Self-injurious behavior</div></div>
Central Apnea	Careful post-operative and post- sedation monitoring	Careful post-operative and post- sedation monitoring