

Evaluation of Causes of Death and Autopsy Reviews in Individuals with CdLS

In this study, patients were selected from a database at the Children's Hospital of Philadelphia (CHOP) and a previous database at Jefferson Medical College. Causes of death in 294 of these patients were determined from review of death certificates, clinical records, autopsy reports, hospital records if available, and contact with the family.

Categories of major organ systems were used to assess the causes. The major causes of death included:

- respiratory, which included all primary respiratory infections, including those related to reflux/aspiration, pulmonary embolus (PE) and asthma;
- gastrointestinal (GI), including primary GI infections, GI-volvulus/obstruction (GIVO), and deaths related to surgical correction of GI problems;
- cardiovascular (CV), sub-classified into congenital heart disease (CHD) (born with a heart defect), which includes complications from surgical repairs, and other CV disease;
- neurologic (CNS), including seizures and central apnea;
- accidents;
- sepsis, or overwhelming infection, including infections without identifiable primary source;
- renal (kidney); and
- congenital diaphragmatic hernia (CDH) (a defect in the diaphragm leading to bowel being pushed into the lung cavities).

Results

Causes of death. (Note: only the most common are listed.)

For 32 infants under 28 days of age, the most common cause of death was congenital diaphragmatic hernia.

Of 51 babies from 29 days to one year of age, the most common causes of death were respiratory (17/51), CHD (15/51), and GI (9/51). 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. The majority of



the GI deaths were related to GI and volvulus/obstruction.

One hundred fourteen children between ages one year and 18 years were included in the childhood data set. The three most common causes of death in this group were respiratory (38/114), GI (22/114), and CNS causes (15/114). Other causes included accidents (12/114) and cardiovascular (11/114).

Respiratory deaths were related to reflux/aspiration in 12 cases, bacterial pneumonia in eight cases, and viral infection. GI causes were overwhelmingly related to GIVO (20/22). There were several feeding tube accidents. CNS causes were attributed to seizures in the majority. Again, the majority of the CV deaths were related to CHD. Accidents accounted for a much larger percentage of deaths in this group, as would be typical for all children with or without CdLS.

For the 97 individuals over age 18 years, the main two causes of death were respiratory (31/97), and GI (27/97), with CNS (10/97) a distant third.

Of the respiratory causes, 16 deaths were related to reflux/aspiration, 10 to bacterial pneumonia, and five unspecified. Of the GI deaths, most were attributed to GIVO. CNS deaths 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.

Of the seven CV deaths, two were related to congenital anomalies, and the others to pericarditis, congestive heart failure, myocardial infarction, and cardiomyopathy. There were five cancer deaths in this group: three were esophageal cancers, one stomach cancer, and one unspecified cancer.

Average Age at Death

The average age of death for those who survived the neonatal period was 12 years 9 months; for those who survived past age one, it was 16 years 2 months; and for those who survived past age 18, it was 28 years 2 months. As the group included only patients who were deceased, these numbers should be interpreted only as data representing the age at death and not life expectancy of children with CdLS.

Discussion

The most surprising finding from this data is the percentage of deaths attributable to GIVO. In addition to the deaths described above, there are multiple case reports of non-fatal GIVO successfully treated with colonic resection (surgery of the large bowel). As surgical techniques have improved, so has survival. However, survival depends on timely recognition and intervention.

Many of the cases were unsuspected clinically due to the non-verbal development of many patients, with patients presenting simply with



discolored discharge in their feeding tubes or an increase in self-injurious behavior. GIVO as a significant contributor to overall causes of death in the patients with CdLS underscores the importance of timely recognition and evaluation for obstruction in the patient with any change in behavior, mental status, or GI symptoms. (*Signs of bowel obstruction include sudden onset of abdominal distention or rigidity of the abdomen, vomiting yellow or green bile, increased pain, and/or self-injury.*)

The number of deaths in the CdLS population studied that were related to GIVO (49 cases) far outnumber those in the medical literature (two cases). This may, in part, represent failure to understand this as a cause of death 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 in later years has allowed them to survive to an age when GIVO is more common.

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 patients with CdLS seem more susceptible to life-threatening respiratory infections. Indeed, many reports in the existing medical literature suggest that people with CdLS are more susceptible to infections that are often antibiotic resistant.

To date, no underlying immunologic abnormality is known in patients with CdLS; however, anomalies of the thymus (an organ of the immune system that is located in front of the heart and behind the sternum) were noted on 8/31 of the autopsies (nearly 25 percent). This raises the possibility of an underlying immunologic abnormality as a contributing cause, and more research is clearly needed on this subject. In addition, five of the autopsies reported anatomic abnormalities of the lungs, raising the question of these abnormalities leading to increased susceptibility to infection.

The impact of reflux is also seen in the incidence of reflux-related cancers, with esophageal cancer listed as the cause of death in three cases and stomach cancer in one case. Our data underscores a need for aggressive management of reflux—which is present in close to 100 percent of



individuals with CdLS—in these patients, as well as timely intervention, antibiotic treatment, and organism identification in all cases of respiratory infection.

Some of the most unnerving deaths in the cases presented are those in which a seemingly healthy, or recovering, child dies suddenly from causes related to apnea/central hypoventilation (stopping breathing).

Two published cases describe episodes of apnea in patients with CdLS: the apnea death of a 21-

year-old man following a dental procedure and a one-month-old infant who experienced non- fatal respiratory arrest lasting several minutes during an orthodontic impression for cleft palate. Another case reports seizures provoked by obstructive apnea in a child with CdLS. This child did not respond to anti-epileptic medications and his seizures stopped with correction of his upper airway obstruction.

These cases highlight 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, with accidents accounting, in part, for 15 deaths in our sample (5.1 percent), compared to 4.7 percent of deaths in the general population (2004).

Increased pain tolerance and lack of communication skills to describe pain and discomfort may lead to accidents involving feeding tubes and bath scalding, especially in institutions where caregivers are 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 nine of the deaths in the study group were directly related to withdrawal of medical care, although they are listed under the primary cause of disease (i.e., pneumonia leading to intubation).

Twenty seven deaths were related 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; however, these deaths underscore the importance of timely recognition of medical problems and special attention, as well as initiating end-of-life discussions among family members.

Prospective studies will be needed to assess the value of these interventions in the health outcomes for this population. In the meantime, they seem





CdLS Foundation

Cornelia de Lange Syndrome Foundation, Inc.

prudent given the specificity and prevalence of the adverse outcomes and contribution to morbidity and mortality observed in the study.

If you have questions or concerns about the study findings, speak with your child's doctor or call the Foundation at 800.753.2357.

This article is derived from a longer paper written by Drs. Ilana Scherer and Samantha Schrier with other members of Dr. Ian Krantz's group at the Children's Hospital of Philadelphia. Lynn Audette at the CdLS Foundation gathered medical records and autopsy reports and provided contacts for Dr.

Jackson, who assembled these materials for the research. Dr. Antonie Kline edited this final article.

REACHING OUT. PROVIDING HELP. GIVING HOPE.

CdLS Foundation | 302 West Main Street, #100 | Avon, CT 06001 | www.CdLSusa.org

