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Addressing the causes of late mortality in infants with congenital diaphragmatic hernia

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ABSTRACT

Introduction: Despite improvements of neonatal intensive care, mortality among patients born with congenital diaphragmatic hernia (CDH), remains high, and there is a significant late mortality in this cohort.
Objective: The aim of this study was to evaluate the causes of death among 251 consecutive CDH patients treated at our institution during the last 26 years period.
Methods: Retrospective review of all causes of death between 1990 and 2015 of the CDH cohort prospectively collected in a database.
Results: Of the 251 CDH patients treated in our department since 1990, 49 were not alive by the end of 2015. Thirty-six patients (14%) died before discharge, and 13 (5%) after the first care event. The mean age at death was 262 days (±653 days, median 34 days). Eighty six % (42 cases) of the fatalities occurred during the first year of life, more than half of the patients died before 1 month of age and only 13% after the age of 1 year (7 patients) (late mortality). The causes of early mortality (before 1 year of age) were mainly cardio-respiratory, whereas GI complications occurred in the late mortality group.
Conclusion: The most common cause of death among CDH patients is respiratory insufficiency and associated pulmonary hypertension, and most of the fatalities occur before 1 year of age. Among older patients, gastrointestinal morbidity as cause of death is highly represented.
Level of evidence: II.

Overall survival rates in patients with congenital diaphragmatic hernia (CDH) have improved over the last decades and are now 70–90% [1]. The improved survival is because of increased use of standardized protocols, the use of gentle ventilation strategies, permissive hypercarbia, extracorporeal membrane oxygenation (ECMO) and concentration of patients to high-volume centers [1–3].

In Stockholm a survival to discharge of 85% was reported in 2012 [4]. In the same study a late mortality rate of 5.4% was reported. Since 1990, the postnatal management for CDH patients in our institution was standardized, with implementation of preoperative stabilization and delayed surgery, permissive hypercarbia and gentle ventilation and the use of ECMO when needed [3]. Criteria for ECMO at our institution follow the international recommendations [3]. The pharmacologic algorithm for the treatment of pulmonary hypertension has evolved during the past decades with the availability of new drugs in the recent years. Since 2008, we implemented a structured follow-up program, according to the recommendations of the American Academy of Pediatrics [5].

However, and despite the improvements in neonatal intensive care and accessibility to new drugs to treat the pulmonary hypertension, mortality among CDH patients remains high, and there is a significant long-term morbidity and mortality in this cohort. The causes of late mortality have not previously been closely studied and there are only a few studies that have reported this sporadically [6–8].

1. Objective

The aim of this study was to evaluate the causes of death among 251consecutive CDH patients treated at our institution during the last 26 years period, and focus in describing the causes for late mortality (defined as fatality occurring beyond 1 year of age) and the risk factors associated with it.

2. Methods

Retrospective review of all causes of death among the CDH cohort treated at our department between 1990 and 2014 was prospectively collected in a database.

Data for the entire cohort was gathered from the department's own database containing all CDH patients treated at our institution since 1990, and contains data such as need for ECMO, time of intubation, use of patch, date of death, etc. Patients that were not alive by the end of 2015 were included in the study. Medical records for these patients were then retrospectively collected from the hospital computerized

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medical record system. The medical records were carefully reviewed regarding a wide range of parameters. When medical records were lacking or the patient was discharged to another caregiver the records were retrieved from other hospitals and/or county archives. Comparisons were made with the cohort of CDH survivors treated at the same institution during the same time period. All data was gathered in a coded Microsoft Excel 2011 file.

Frequencies were reported for categorical variables, median and mean ± standard deviation (SD) for continuous variables. SPSS® version 22 and PRISM 6 (Graphpad Software Inc) were used for statistical analyses and figures. Mann–Whitney test was used for continuous variables and chi-square test for categorical variables. Fisher's exact tests were used for dichotomous variables. A p-value of less than 0.05 was considered statistically significant.

Ethics permit from the central ethical review board in Stockholm, Dnr 2014/2041–31.

3. Results

Of the 251 CDH patients treated in our institution between 1990 and 2014, 49 were not alive by the end of 2015 (Fig. 1). The overall mortality rate for the entire cohort was 19%. Thirty-six patients died before discharge (14% mortality to discharge, 73% of the total mortality), and 13 fatalities occurred after the first care event (5% mortality after discharge, 27% of the total mortality). Out of these 13 patients who died after discharge, 7 patients deceased after the age of 1 year (2.8% late mortality, 14% of the total mortality). The mean age at death was 262 days (±653 days, median 34 days). There were no differences in gender distribution or side of the defect between the surviving or deceased patients. There was a higher rate of prenatal diagnosis, ECMO need and need for patch repair in the group of patients that did not survive, and the majority of those patients were intubated within 6 h of life (Table 1). All hernias in this cohort were repaired through laparotomy.

Forty-two patients died before 1 year of age, and the causes of death were mainly cardio-respiratory.

Thirteen patients died after discharge of which 6 died before 1 year of age. The later died because of progressive cardio-respiratory deterioration.

3.1. Late mortality

Seven patients died after 1 year of age. The cause of death was progressive respiratory insufficiency in 2 cases, persistent pulmonary hypertension in 2 cases, and gastrointestinal (GI) related complications in three cases (Table 2). Three out of 7 patients were inborn, and CDH prenatally diagnosed in 3/7 cases. The majority (5/7) were boys and left sided CDH (6/7). Liver was up in 86% of the cases, patch repair

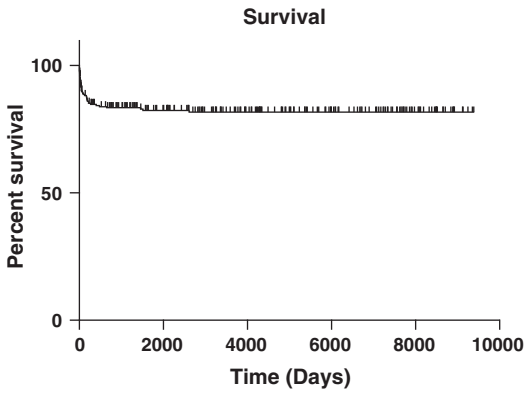

Fig. 1. Survival curve for the CDH cohort.

Table 1
Patient's characteristics of the entire CDH cohort Fisher's test, $p < 0.05$ significant.

	Survivors	Early mortality (<1 year)	Late mortality (>1 year)
n	202	42	7
Prenatal diagnosis (%)	33	85	42
Male (%)	60	77	71
Intubation <6 h (%)	66	98	86
Left side (%)	86	70	86
Patch (%)	36	51	57
ECMO (%)	25	58	57
ECMO 2nd run (%)	4	13	42
Age at death mean/median (days)		64/25	1509/1461

was needed in 57% of the cases, and 57% of the patients required ECMO support, 3 of the patients requiring ECMO twice (Table 3). There was no significant age difference among patients dying from GI causes (median 1483 days) compared to those who died because of cardio-respiratory problems (median 1633 days) (Fig. 2). GI complications leading to death were incarceration of the colon in the thorax after recurrence of the diaphragmatic defect at age of 1 year in one patient (patient 5 in Table 2), intestinal obstruction because of adhesions and fibrous band that caused volvulus and obstruction of the mesenteric superior artery at the age of 3 years and 11 months in another patient (patient 6 in Table 2) and malrotation and volvulus at the age of 4 years in the last case (patient 7 in Table 2). Only one of the patients in this group required ECMO treatment, and in one case CDH was diagnosed at 3 months of age (Table 2). Patients 5 and 7 had a medical history of recurrent abdominal pain, vomiting and constipation, whereas patient 6 had no major GI complaints until sudden onset of abdominal pain and shock.

Other GI surgery was common in this group of patients who died after 1 year of age, with 71% (5/7) of patients requiring surgery for bowel obstruction or gastrostomy-tube insertion.

Forty-three percent (3/7) of the patients in the late mortality group had a recurrence of the defect found at post-mortem studies, compared to a recurrence rate of 3% in the cohort who survived prenatally diagnosed CDH, as previously reported [9]. Two of the cases that recurred died of GI causes and one due of progressive respiratory insufficiency and severe pneumonia. In the last patient, re-operation because of recurrence at the age of 8 months was performed. The patient suffered another relapse with herniation of the stomach to the left hemi-thorax, but this was not diagnosed, and most likely contributed to the clinical deterioration that the patient experienced during the last months, and could have been a contributor to the severe pneumonia with aspiration that was the determinant cause of death (patient 2 in Table 2). Of the 3 cases that recurred, patch was used in 2 and 1 was primarily closed. They were all left sided (Table 2).

The overall mortality of CDH patients treated on ECMO was 42% (33/80). Four of these (4/80, 5%) occurred after one year of age. Late mortality rates of patients not treated with ECMO were 1.8%. We found a higher odds of suffering of late mortality if ECMO treatment was needed in the neonatal period; OR 5.2, 95% CI (1.1–24.2) ($p = 0.03$).

There was no correlation between dying from intestinal complications and the use of patch ($p = 0.545$) and no correlation between presence of patch and other surgery of the bowel ($p = 0.242$). There was neither any correlation between having repeated surgery of the bowel and dying from intestinal causes ($p = 1$).

Several of the patients in the late mortality group had neurodevelopmental delays. Some had other neurological sequelae such as strabismus, epilepsy and motor delays. Failure to thrive was present with a varying degree of reporting in the records of the late mortality group. Growth and weight gain was delayed in about half of the patients. Three patients had problems with gastroesophageal reflux (GER) and vomiting. One of these needed a jejunostomy and two a gastric tube.