Differences in Outcomes in Prenatally Diagnosed Congenital Diaphragmatic Hernia Compared to Postnatal Detection: A Single-Center Experience

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Key Words

Congenital diaphragmatic hernia · Observed to expected lung-to-head ratio · Extracorporeal membrane oxygenation

Abstract

Objectives: To compare outcomes in pregnancies with a prenatal detection of congenital diaphragmatic hernia (CDH) with children diagnosed after birth, treated at the same institution, and to determine the ability to predict prognosis through measurements of the observed to expected lung-to-head ratio (O/E LHR). **Methods:** This is a retrospective review of all children with CDH treated at our institution during 2006–2014. We compared outcomes of infants referred for surgery after postnatal diagnosis with outcomes of infants with prenatally diagnosed CDH. **Results:** In the prenatal group, O/E LHR was significantly different between survivors and deceased patients, with a cutoff at 35% O/E LHR. Survival to discharge and 1-year survival were significantly higher in the postnatal group that required intubation within 24 h; i.e., 92 and 89% versus 85 and 73% in the prenatal group ($p < 0.05$). There was less need for extracorporeal membrane oxygenation (ECMO), 41 versus 60%, and patch, 41 versus 75% ($p < 0.001$), in the postnatal group with early diagnosis compared with the prenatal group, respectively. **Conclusion:** Children with prenatally diagnosed CDH

represent a population with a more severe condition compared to infants diagnosed after birth. They have poorer outcomes with higher needs for ECMO or use of patch, and lower survival rates were observed at an O/E LHR below 35%.

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Introduction

Congenital diaphragmatic hernia (CDH) is a complex malformation, with concomitant anomalies of diaphragm, lung and vascular development. Despite substantial progress in neonatal intensive care, it remains one of the most challenging and potentially life-threatening diagnoses in pediatric surgery [1]. CDH causes pulmonary hypoplasia and abnormal pulmonary vasculature, which causes vasoconstriction and altered vasoreactivity in the pulmonary vessel bed leading to respiratory insufficiency [2]. However, the individual heterogeneity in these effects makes it difficult to accurately predict outcomes [3, 4]. Patient stratification according to CDH severity is not always reported [5–7]. The overall prenatal detection rate of CDH with ultrasound is approximately 60%. The prenatal detection depends on the number of scans and the timing of these during pregnancy. There is no particular group of women with an increased risk of

this malformation, which means that the detection of affected fetuses occurs at the time of screening or late in the third trimester if polyhydramnios develops [8]. Prenatal diagnosis allows for counseling and delivery planning at a tertiary center. Even though studies indicated that infants with a prenatal diagnosis of CDH represent a group with worse outcome already 2 decades ago, there have been reports from other institutions that could not observe any differences in long-term outcomes or survival [9, 10]. These differences are believed to be due to variable degrees of pulmonary hypoplasia depending on the duration of compression exerted by the viscera [10, 11].

The objective of the current study was to investigate if these differences in outcome still persist with current treatment with recent advances in intensive care and surgical skills as well as to determine any predictors of outcome in prenatal cases managed at the same institution.

Methods

The study is a retrospective review of all cases of CDH managed at our institution during the period 2006–2014. Medical records including ultrasound reports from all the pregnancies and infants born with CDH were reviewed. Data on patient demographics, prenatal imaging, gestational age at birth, mode of delivery, surgical management, associated structural and chromosomal anomalies, need for patch repair, treatment with extracorporeal membrane oxygenation (ECMO), survival, postoperative short- and long-term complications, and length of hospital stay were obtained from patient records.

We divided the cases included in the study into 2 groups depending on when the diagnosis of CDH was done, pre- or postnatally. In the prenatal group, we included all cases of CDH that were managed at our Fetal Medicine Unit during pregnancy and treated at the Department of Pediatric Surgery after birth, but also cases of CDH that were managed prenatally at other institutions, and later referred to our institution for ECMO treatment during 2006–2014. In the subgroup of pregnancies with prenatally diagnosed CDH managed at our Fetal Medicine Unit, we collected detailed data concerning their prenatal examinations. The observed to expected lung-to-head ratio (O/E LHR) was measured at 3 occasions during pregnancy: at the time of detection, in the late-second trimester and in the third trimester prior to delivery using the longest axes of the lung size contralateral to the affected side at the level of the four-chamber view [12]. In the postnatal group, we included all newborns referred to the Pediatric Surgery Unit for treatment lacking a prenatal diagnosis during the same time period. We later analyzed the data dividing it into subgroups of patients where the diagnosis of CDH was done immediately after birth, excluding those with a diagnosis made later than 3 days of life and those that required intubation within 24 h of life, and compared their outcomes with the prenatal group.

The postnatal management of CDH patients at our institution has been standardized since 1990, with implementation of preoperative stabilization and delayed surgery, permissive hypercarbia

and gentle ventilation and the use of ECMO when needed [13]. Our criteria for ECMO include the inability to maintain preductal saturation >85% or postductal saturation >70%, increased PaCO₂ and respiratory acidosis with pH <7.15 despite the optimization of ventilator management, peak inspiratory pressure >28 cm H₂O or mean airway pressure >17 cm H₂O required to achieve saturation >85%, metabolic acidosis with lactate >5 mmol/l and pH <7.15, systemic hypotension resistant to fluid and inotropic support resulting in urine output <0.5 ml/kg/h or oxygenation index >40. The pharmacologic algorithm for the treatment of pulmonary hypertension starts with inhaled nitric oxide when there is evidence of extrapulmonary right-to-left shunting and oxygenation index >20 and/or >10% saturation difference. If there is no or an insufficient response to inhaled nitric oxide, treatment should be scaled up with intravenous sildenafil (phosphodiesterase 5 inhibitor), followed by intravenous prostacyclin. Endothelin antagonist Bosentan[®] and tyrosine kinase inhibitor Imatinib[®] have also been used in cases with intractable pulmonary hypertension unresponsive to the above-described treatment algorithm [14]. Since 2008, we have followed up our patients with a structured follow-up program, similar to the recommendations of the American Academy of Pediatrics [15].

Statistical analysis was performed using the χ^2 and Fisher's exact tests for categorical variables, and linear regression and goodness-of-fit analysis with p values <0.05 considered as significant. All data analyses were conducted using GraphPad Prism 6.0 (La Jolla, Calif., USA).

The study was approved by the regional ethics board, local committee of North Stockholm (Dnr 2014/2041-31).

Results

A total of 98 cases with CDH were managed at the pediatric surgical unit during the 9-year period. In 53 cases, the diagnosis was known before birth, but only 36 cases were followed at our Fetal Medicine Unit, and 17 cases were managed and followed prenatally at other institutions and referred to our ECMO unit after birth. In 45 cases, the condition was first diagnosed after birth. Of these, 33 cases were diagnosed immediately after birth, and 12 cases had a later diagnosis (range 12 days to 3 years; mean 330 days, median 8.5 months).

Prenatally Diagnosed CDH

Seventy-nine percent of the cases had left-sided CDH, 17% right-sided CDH and 4% bilateral CDH. All 53 cases with prenatally diagnosed CDH were intubated immediately after birth. Five patients with prenatally diagnosed CDH were born abroad and transferred to our institution with our mobile ECMO team [16] after birth for ECMO support. These patients are included in the data regarding the first care event and survival to discharge, but excluded from long-term data. The overall survival in the prena-

Fig. 1. **a** Number of patients with severe (O/E LHR <25%), moderate (O/E LHR 26–35%), mild-to-moderate (O/E LHR 36–45%) and mild lung hypoplasia (O/E LHR >46%) who survived or deceased. **b** Survival rates in relation to O/E LHR and liver position. **c** ECMO needs in relation to O/E LHR. **d** Long-term morbidity in relation to O/E LHR.

tally diagnosed group was 85%, and the long-term survival was 73%. Sixty percent of the patients required ECMO support, with survival rates of 67%. Over 75% of the cases required patch repair. The survival rate for right-sided prenatally diagnosed CDH was 100%.

Of the 36 patients with a prenatal diagnosis followed at our Fetal Medicine Unit, 58% were boys and 42% were girls. Sixty-five percent were delivered with planned cesarean section, 20% with emergency cesarean section and 15% with a vaginal delivery. The mean gestational age at diagnosis was 22.6 ± 6.1 gestational weeks (GW). Sixty percent were diagnosed before 22 GW, representing the upper limit for termination of pregnancy in Sweden, 40% later than 22 completed weeks. Two cases, 1 with right-

sided and 1 with bilateral CDH, underwent fetal surgery with fetoscopic endoluminal reversible tracheal occlusion (FETO) at 29 GW, followed by removal of the balloon 4 weeks later. The mean birth weight was $3,078 \pm 530$ g, and the mean gestational age at delivery was 37.5 ± 1.4 GW. In 28 (78%) cases, the defect was left-sided, in 6 (17%) right-sided and in 2 (5.5%) bilateral. Eight patients had severe lung hypoplasia with O/E LHR <25% and liver-up in 7/8 cases, 5 patients had moderate lung hypoplasia with O/E LHR 26–35% and liver-up, 10 patients had mild-to-moderate lung hypoplasia with O/E LHR 36–45% and liver-up in 5/10 cases, and 13 cases were assessed to have mild lung hypoplasia with O/E LHR >46% and liver-up in 9/13 cases (fig. 1a). In 3 cases only, palliative care was

Fig. 2. Significantly different O/E LHR (mean $\pm$ SD) between survivors and deceased cases, at all three observations during 21, 29 and 34 GW.

provided after birth, and these infants did not undergo surgery due to the poor prognosis (2 patients with bilateral hernias and 1 patient with trisomy 18). The remaining 33 cases were intubated within 6 h after birth. The overall survival rate to discharge was 78% ($n = 28$), and there was a late mortality rate of 5.5% ($n = 2$).

Polyhydramnios was observed prenatally in 6 cases (17%), and all of these patients survived. Associated anomalies were found in 8 patients: 2 patients with congenital cystic adenomatoid malformations, 1 with bronchopulmonary sequestration, 1 with dysmelia, 1 with polydactyly, 1 with hydronephrosis, and 2 patients with cardiac anomalies (ventricle septum defects). Associated chromosomal aberrations were found in 2 patients (trisomy 18 in 1 patient and mosaic trisomy 9 in 1 patient).

All cases with right-sided CDH survived, both infants with bilateral CDH died, and the survival rate for left-sided CDH was 70%. O/E LHR was significantly higher at all 3 observational occasions during pregnancy in the group of surviving patients (fig. 2). In the group with severe pulmonary hypoplasia and O/E LHR $<25\%$, the survival rate was 25%; in the moderate group with O/E LHR 26–35%, the survival rate was 40%; in the mild-to-moderate group with O/E LHR 36–45%, the survival rate was 100%, and in the mild group with O/E LHR $>46\%$, the survival rate was 92% (fig. 1b). Liver-up was found in 72% of cases, with a survival rate of 69%. A patch was used in 75% of the cases, with a survival rate of 65%. The overall need for ECMO was 42%, with a 54% survival rate. Fifteen

percent of cases had a second ECMO run, with only 33% surviving (table 1). The need for ECMO increased with the severity of the condition (fig. 1c). Sixty-seven percent had pulmonary hypertension that required medical treatment. In 11% of the patients, the stomach was down, and all these cases survived. The recurrence rate of diaphragmatic hernia was 2.9%. Among survivors, 25% had significant pulmonary morbidity, 15% gastrointestinal morbidity, 15% neurological morbidity and 10% musculoskeletal morbidity. Despite the severity of the condition, none of the survivors in the more severe groups had any significant long-term morbidity (fig. 1d).

Two cases, 1 with right-sided and 1 with bilateral CDH, underwent fetal surgery with FETO at 29 GW, followed by removal of the balloon 4 weeks later. The case with right-sided CDH had lung volumes of 15 and 50% prior to and after FETO treatment, respectively, was born at 39 GW and did not require ECMO but patch repair. The case with bilateral hernia was born at 36 GW, but due to the lack of lung growth after fetal intervention, only palliative care was provided after birth and the infant deceased 2 h after birth.

Postnatally Diagnosed CDH

Of the 45 patients with a postnatal diagnosis, 60% were boys and the majority were delivered through vaginal birth (75%); only 6% with planned cesarean section and 19% with emergency cesarean section. The mean birth weight was $3,216 \pm 713$ g, and the mean gestational age at birth was 38.4 ± 3.1 GW.

The majority of the defects were left-sided (84%), 16% ($n = 7$) were right-sided, and there were no cases of bilateral hernia. Forty-two percent were intubated within 6 h of life, 17% were intubated between 6 and 24 h of life and 40% after 24 h of life. Twenty-four percent of the patients required ECMO. All patients underwent surgical repair. The overall survival rate to discharge was 96% (43/45), and the late mortality rate was 2.3% (1/43).

The survival rate was 97% (37/38) for left-sided defects and 71% (5/7) for right-sided defects. The liver was up in 29% of the cases. Patch repair was needed in 27% of cases, with 75% survival in this group. All patients intubated later than 6 h of life survived. The survival rate for patients treated with ECMO was 73%. In 6.6% (3/45) of the cases, ECMO was required twice, with 1 patient surviving in this group (table 1).

Among survivors, 13% had some respiratory symptoms, 11% gastrointestinal morbidity and 11% neurological disability at follow-up. No patient in this group had significant musculoskeletal morbidity.

Table 1. Patient characteristics and outcome for prenatally versus postnatally diagnosed CDH

	Prenatally diagnosed CDH			Postnatally diagnosed CDH			OR (95% CI)	p value
	inborn	outborn	all	all	early diagnosis	intubation <24 h		
Patients	36	17	53	45	33	27		
Birth weight, kg	3.1±0.5	2.9±0.7	3±0.6	3.2±0.71	3.2±0.6	3.2±0.6		n.s.
Gestational age at birth, weeks	37.5±1.4	37.1±2	37.3±17	38.4±3.1	38.1±3	38.07±3.4		n.s.
Survival to discharge	78 (28)	100	84.9 (45)	96 (43)	94 (31)	92.6 (25)		
Long-term survival	72 (26)	75 (9) ^a	72.9 (35)	93 (42)	89.9 (30)	88.9 (24)	0.26 (0.07–1.036)	0.05
Age at intubation								
<6 h	100	100		42	54.5			
6–24 h				17	21.2			
>24 h				42	21.2			
<24 h						100		
ECMO	42 (15)	70.6 (12)	50.9 (27)	24 (11)	33.3 (11)	40.7 (11)	3.04 (1.7–5.4)	0.0001
Survival ECMO	54 (8)	83.3 (10)	66.6 (18)	73 (8)	72 (8)	72 (8)		
ECMO 2nd run	17 (6)	17.6 (3)	16.98 (9)	6.6 (3)	9 (3)	11 (3)		
Survival ECMO 2nd run	33 (2)	66.6 (2)	44.4 (4)	33 (1)	33 (1)	33 (1)		
Patch repair	75 (27)	76.5 (13)	75.4 (40)	27 (12)	36.3 (12)	40.7 (11)	5.3 (2.09–13.87)	0.0006
Survival patch repair	74 (20)	76.9 (10)	75 (30)	75 (9)	75 (9)	72 (8)		
Left-sided CDH	75 (27)	88.3 (15)	79.2 (42)	84 (38)	88 (29)	88.9 (24)		n.s.
Right-sided CDH	19.5 (7)	11.7 (2)	16.98 (9)	16 (7)	12.1 (4)	11 (3)		
Bilateral CDH	5.5 (2)		3.8 (2)	0				
Survival								
Left-sided CDH	77.8 (21)	80 (12)	78.5 (33)	97 (37)	97 (28)	96 (23)	0.13 (0.01–1.09)	<0.04
Right-sided CDH	100	100	100	71 (5)	50 (2)	33 (1)	31.6 (0.96–1,040)	<0.04
Bilateral CDH	0		0					

Values are presented as means ± SD or percentages with numbers in parentheses. Comparisons are made between all prenatally diagnosed CDH patients and the subgroup of patients with early postnatal diagnosis and intubation within 24 h of life. $p < 0.05$ is considered significant. n.s. = Not significant.

^a Five living abroad were excluded.

When analyzing the subgroup of patients where the diagnosis was made immediately after birth, 55% of the cases were intubated within 6 h of life and only 21% after 24 h. Survival to discharge was 94% and long-term survival was 90%. The survival rate for right-sided CDH was 50% (2/4) in this subgroup. The need for ECMO was 33%, with 72% surviving and 36% requiring a patch to close the defect. In the subgroup of patients who required intubation within 24 h of life, survival to discharge was 92% and long-term survival was 89%. In this subgroup, the survival rate for right-sided CDH was only 33%, with similar rates for ECMO need and patch repair (41%) (table 1).

When comparing the entire group of prenatally diagnosed CDH with the subgroup of patients with postnatal diagnosis who required intubation within 24 h after birth, there were no differences in gestational age or birth

weight. There was a significantly higher survival rate in the postnatally diagnosed group ($p = 0.04$) and a greater need for patch in the prenatally diagnosed group ($p < 0.0006$; OR 5.3, 95% CI 2.09–13.8), and ECMO support ($p = 0.0001$; OR 3.04, 95% CI 1.7–5.4).

Cases with right-sided CDH diagnosed after birth had a significantly worse outcome than cases with a prenatal diagnosis: 50% (2/4) versus 100% (6/6) ($p < 0.04$; OR 31.6, 95% CI 0.96–1,040; table 1; fig. 3).

Discussion

A prenatal diagnosis of CDH conveys a worse prognosis compared to a postnatal identification of the same condition.

Fig. 3. a Long-term survival and survival for right-sided CDH in the prenatally and early postnatally diagnosed group. **b** Need for ECMO and patch repair in both groups ($p < 0.05$).

In this study, we could observe that still today, despite current improvements in the basic knowledge of the natural history of the disease, in the planned delivery at perinatal centers with pediatric surgical expertise and immediate resuscitation of the affected child as well as the option of fetal surgery, prenatal diagnosis will imply a significantly worse prognosis compared to a postnatal diagnosis in children with the same condition. This is believed to be caused by the timing and duration of herniated abdominal organs and the mass effect of these leading to variable degrees of pulmonary hypoplasia [17]. The better survival in the cases with a postnatal diagnosis may be explained by herniation occurring late during pregnancy or because of small hernias that were missed at the time of prenatal ultrasound screening in the second trimester [18]. Also, more severe cases and those with associated structural and chromosomal anomalies will most likely have been terminated following prenatal detection, resulting in relatively good survival rates. All the patients in our study were managed at the same institution, by the same staff and with similar indications for patch repair and ECMO. Yet, outcomes in terms of both short- and long-term survival as well as need for patch repair were significantly different, which strengthens our observations. It seems clear that the extent of pulmonary hypoplasia at the time of birth is still the single most important factor determining survival and morbidity in children

with CDH [1, 4]. Tracheal occlusion through FETO is the only clinically available treatment option that can reduce pulmonary hypoplasia and offer lung growth during the window of opportunity in the third trimester of pregnancy if the condition is identified and properly assessed [19]. A cutoff O/E LHR below 35% at prenatal evaluation was predictable for poorer outcomes in our series, in line with previous studies [12]. At our institution, the survival rate was below 50% in this group, but notably, surviving infants had no long-term morbidity, indicating that survival in the intensive care unit was not pursued at all costs (fig. 1d).

FETO has been reported to increase survival in cases with severe CDH from 24 to 49% [20], and there are currently two ongoing randomized controlled trials for moderate (O/E LHR 25–45%) and severe (O/E LHR <25%) lung hypoplasia (<https://clinicaltrials.gov/ct2/show/NCT00763737>). If the ongoing RCTs confirm the excellent preliminary results from intrauterine intervention through FETO, there will be a need for implementing this new strategy in the clinical management of CDH patients.

Interestingly, we found a significantly better outcome for patients with right-sided CDH who were diagnosed prenatally compared to those with a right-sided defect diagnosed after birth. While the reason for this observation is unclear, we speculate that due to the difficulties in making the diagnosis of right-sided CDH, through failure to

discriminate between liver and lung parenchyma, many of these right-sided defects are missed at the time of the second trimester scan [21, 22].

Therefore, if the prenatal diagnostic accuracy had been similar to that of cases with left-sided CDH, some of the right-sided hernias in our postnatal cohort should have been in the prenatal group, thereby alleviating the differences that we observed between the two groups.

Even though our findings of better overall survival rates for postnatally diagnosed CDH support the fact that prenatally diagnosed CDH represents a more severe condition, there may be a selection bias of patients diagnosed postnatally with a more severe condition who would thus

never reach our pediatric surgical unit. We observed better outcomes in outborn cases with prenatally diagnosed CDH compared to inborn cases, which could probably also be explained by a selection bias of more stable patients that could be transferred to our surgical unit after birth.

In summary, children born with CDH having a prenatal diagnosis represent a population with a more severe condition compared to treated infants with a postnatal diagnosis. They have considerably poorer outcomes with higher needs for ECMO, use of patch and lower survival rates. Risk for poorer survival was possible to predict when O/E LHR was below 35% at prenatal evaluation.

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