Congenital Diaphragmatic Hernia: 22 years Experience in a Single Tertiary Medical Center

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Key words: congenital diaphragmatic hernia, prenatal diagnosis, neonatal mortality, right-side congenital diaphragmatic hernia, termination of pregnancy

Abstract

Background: Over the last two decades, the epidemiology, treatment strategy and mortality rate for congenital diaphragmatic hernia have changed.

Objectives: To retrospectively analyze our experience with CDH of the last 22 years.

Methods: We reviewed the charts of all infants suffering from CDH between 1985 and 2007. Prenatal and maternal as well as perinatal and neonatal data were collected, including outcome parameters. The 71 infants that we identified were divided into two historical groups: from 1985 to 1995 (group 1, 23 patients) and from 1996 to 2007 (group 2, 45 patients).

Results: There was an increase in the incidence of prenatal diagnosis and a subsequent significant decrease in gestational age at diagnosis in group 2 (25 weeks gestation, compared with 30 weeks gestation in group 1, $P = 0.018$). In addition, we noted a trend toward a reduced number of infants with right-sided hernia and associated cardiac anomalies. The timing to post-delivery surgery was significantly longer in group 2 (20 hours in group 1 vs. 53 hours in group 2, $P < 0.001$). A significant reduction in postoperative mortality was demonstrated in group 2 compared with group 1 (13.5% vs. 38.7% respectively, $P = 0.04$),

Conclusion: Our data suggest a higher survival rate for operated infants in group 2 during the last decade, probably due to changes in preoperative methods of treatment as well as later surgery timing compared to group 1. We speculate that today's cases of congenital diaphragmatic hernia are probably milder than in the past due to earlier and more detailed prenatal diagnosis and subsequent termination of pregnancies for the more severe forms of the disorder.

IMAJ 2008;10:880–883

Congenital diaphragmatic hernia is present in approximately 1 of every 2500 live-born neonates [1]. The prognosis of CDH is related to pulmonary hypoplasia as well as primary abnormality of airway branching, combined with the coexistence of other major malformations [2]. The disorder is no longer thought to require immediate surgery, and new modes of preoperative treatment have led to an incremental increase in survival rate.

CDH = congenital diaphragmatic hernia

The current study retrospectively reviewed our institution's experience in the management and surgical outcome of CDH over the last 22 years. We analyzed the data by comparing two time periods, 1985–1995 and 1996 to the present. We selected these dates because, starting in 1995, neonatal critical care improved and new strategies were introduced, such as permissive hypercapnia, gentle ventilation strategy with high frequency, nitric oxide and extracorporal membranous ventilation.

Patients and Methods

Cases of CDH were selected from hospital discharge records, based on the International Classification of Disease, 10th Revision, Clinical modification (ICD-10) code 756.6, "anomalies of the diaphragm." Seventy-one patients treated at the Sheba Medical Center between 1985 and 2007 were identified. Excluded were children who were asymptomatic postnatally and those diagnosed over the age of 1 month since this unique situation represents a distinct clinical course.

Two periods were considered, the first from 1985 to 1995 comprising 23 patients (group 1) and the second from 1996 to 2007 comprising 45 patients (group 2). Since 1996, our institute adopted a standardized approach to newborn infants with CDH. This strategy includes planned delivery at term or near term, immediate intubation, nasogastric tube (active suction), sedation and gentle ventilation strategy. Surgical repair was delayed as required until the infant was hemodynamically stable.

The main data analyzed included gestational age at intrauterine diagnosis, gestational age at birth, inborn or outborn, gender, presence of associated congenital anomalies, presurgical ventilation parameters, timing of surgical repair, site of the diaphragmatic defect, and description of the abdominal organ herniation. Cases were also classified according to treatment outcome, including death and length of hospitalization. The study was approved by the ethics committee of the Sheba Medical Center.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS), version 14.0, was used to analyze the data. Continuous parameters

Table 1. Characteristics of 68 patients with CDH

	Group 1 (23 patients)	Group 2 (45 patients)	*P*
Inborn, n (%)	23 (100%)	37 (82.2%)	0.044
Gestational age (wks), mean ± SD	38 ± 4	38 ± 2	0.768
Gender, M/F	17/6	29/16	0.585
Birth weight (g), mean ± SD	2703 ± 903	2874 ± 627	0.420
Established prenatal diagnosis, n (%)	11 (47%)	33 (73%)	0.06
Prenatal diagnosis (wks), mean ± SD*	30.73 ± 5.9	25.55 ± 6.1	0.018
Side of the diaphragmatic defect, Lt/Rt	15/8	38/7	0.12
Associated major malformations, n (%)**	2 (8.7%)	3 (6.5%)	1.000
Cardiac malformation, n (%)	5 (21.7%)	3 (6.7%)	0.109

* Relates only to cases with established prenatal diagnosis

** Non-cardiac

Table 2. Management and outcome analysis

Management and mortality	Group 1 (23 patients)	Group 2 (45 patients)	*P*
Preoperative mechanical ventilation, n (%)	21 (91.3%)	42 (93.3%) *	0.572
Surgery performed, n (%)	18 (78.3%)	37 (82.2%)	0.750
Surgery timing: birth to operation (hr), mean ± SD	20.12 ± 21.12	53.76 ± 3 3.91	< 0.001
ECMO	0	5	< 0.001
Total hospitalization time (days) mean ± SD	38.67 ± 25.28	43.78 ± 45.13	0.713
Preoperative mortality	5/23 (21.7%)	8/45 (17.8%)	0.750
Postoperative mortality	7/18 (38.9%)	5/37 (13.5%)	0.043
Total mortality	12/23 (52.2%)	13/45 (28.8%)	0.069

* In this group two neonates were ventilated using HFV mode

Table 3. Group 2 (late period) – possible predictors for survival

	Died (n=13)	Survived (n=32)	*P*
Prenatal diagnosis (n)	11	22	0.46
Prenatal diagnosis (gestational wks)	25.1 ± 6.4	25.8 ± 6.1	0.765
Associated cardiac malformation, n (%)	1 (7.7)	2 (6/3)	1.000
Associated non-cardiac malformation, n (%)	1 (7.7)	(6/3)	1.000
Right-sided CDH, n (%)	2 (15.4)	5 (15.6)	1.000
Inborn, n (%)	11 (84.5)	26 (81.3)	1.000
Gestational age (wk)	38.46 ± 2.03	37.94 ± 2.16	0.446
Male/female, n (%)	53.8/46.2 (7/6)	68.8/31.2 (22/10)	0.494
Birth weight (g)	2953.16 ± 625.15	2682.00 ± 537.5	0.192
Max peak pressure * (33)	31.29 ± 6.55 (7)	21.31 ± 4.58 (26)	< 0.001
ECMO, n (%)	4 (30.8)	1 (3.1)	0.02
Surgery performed, n (%)	8 (61.5)	32 (100)	< 0.001

* Some data were missing; the number in parenthesis represents cases

were analyzed for normal distribution. Student t-test analysis was performed to compare continuous parameters. Discrete variables were compared using Pearson's chi-square test or Fisher exact test, as appropriate. A *P* value of ≤ 0.05 was considered significant.

Results

Seventy-one patients with CDH were identified in our institute over the last 22 years. Among them three cases were excluded due to late clinical presentation. Demographic data, management and outcome are given in Tables 1 and 2.

A larger number (approaching significance) of infants in group 2 were diagnosed in the prenatal period ($P = 0.06$). The ultrasound intrauterine diagnosis of CDH was earlier in group 2 compared to group 1 (25.55 ± 6.1 versus 30.73 ± 5.9 weeks respectively, $P = 0.018$). In addition, there was a trend towards decreased incidence of right-sided hernia and associated cardiac anomalies in group 2 in comparison to group 1 ($P = 0.12$ and 0.109 respectively). Milder cardiac anomalies, such as secondary atrial septal defect and apical ventricular septal defect, were found in group 2 compared with more severe cardiac anomalies, such as tetralogy of Fallot and Ebstein anomaly, in group 1.

A marked difference was found in the interval between diagnosis and surgical procedure between the two groups [Table 2]. All the patients with CDH who did not undergo surgical procedure died, thus giving a total mortality rate of 52.2% in group 1 compared to 28.8% in group 2 ($P = 0.069$) and a significant reduction in the postoperative mortality rate in group 2 compared to group 1 (13.5% vs. 38.9%, $P = 0.043$).

Factors associated with death among live-born infants in group 2 are presented in Table 3. The need for aggressive ventilation, or ventilation failure requiring ECMO, was associated with high mortality rate.

Discussion

This retrospective study represents the largest single-center study of CDH published in Israel. Our data demonstrate the evolving changes in prenatal diagnosis, treatment strategy and mortality rate of infants with CDH in the last two decades. Of particular significance are the low mortality rates (total and specifically postoperative) in group 2, which are even lower than the rates of mortality in previously published clinical presentations [3,4].

In the current retrospective analysis, we noticed three main clinical presentations of infants with CDH. The first category consists of severely morbid infants who usually needed immediate post-delivery resuscitation and died before surgery could be performed. The second presentation includes moderately to severe decompensated infants who required respiratory support – namely, intubation and ventilation – and reached surgery in an acceptable stable respiratory and hemodynamic condition. This group represents most of our CDH cases. The third group comprises infants with late clinical presentation during their first months or years of life. This clinically based grouping represents different levels of disease severity, probably due primarily to lung decompensated status, which was previously noted to be the most important factor in determining disease outcome [2].

ECMO = extracorporal membranous ventilation

The data from both the earlier and the later groups indicate that infants born during the last decade were more frequently diagnosed prenatally (47.8 vs. 73.3% respectively) and at earlier stages of pregnancy (30.7 vs. 25.5 weeks gestation). Moreover, they had fewer cardiac anomalies (21.7% vs. 6.7%), less right-sided CDH (34.7 vs. 15.5%) and a higher rate of survival. These findings can be attributed to the early detection of intrauterine CDH and increasing number of pregnancy terminations, since cardiac anomalies and right CDH are considered to be poor prognostic factors by many physicians [5-7]. However, some evidence in the literature indicates that right-sided CDH has the same outcome as left-sided CDH [8]. The significant lower number of inborn patients in group 2 in comparison to group 1 (100% vs. 82.2%) may represent a local trend of referring those patients to our center. There is a growing awareness that infants with an antenatal diagnosis of CDH should be delivered at a medical center that offers advanced therapies such as HFV, inhaled nitric oxide, gentle ventilation and ECMO, if necessary [9], to treat these critically ill infants.

Advances in neonatal intensive care and ventilation strategies have greatly improved the outcome of live-born infants with CDH [1]. Data on treatment modalities such as HFV and ECMO are controversial [9,10]. ECMO has been used with varying results. Five infants were treated and operated while on ECMO in our hospital, four of whom died. In all cases ECMO was used as a rescue therapy, which can explain our unfavorable results. A retrospective review of more than 400 infants with CDH at Children's Hospital (Boston, MA, USA) and at The Hospital for Sick Children (Toronto, Canada) compared the outcomes between 1981 and 1994 [5,11]. In the Boston series, ECMO was the predominantly used rescue mode, compared to HFV in Toronto. The survival outcomes at the two institutions were the same (53% vs. 55%). Fifty percent of the infants in the Boston series received ECMO, compared with only 1% in Toronto. A recent Cochrane Review did not demonstrate a definitive improvement in the survival rate with ECMO [12]. These two points cast doubt on whether ECMO is beneficial for treating CDH.

Barotrauma has now been recognized as a significant cause of mortality and morbidity in CDH [10]. "Gentle" ventilation with permissive hypercapnia protocol is designed to minimize barotrauma by strictly limiting the peak inflation pressure. Ventilation is aimed at keeping pre-ductal oxygen saturation above 85%, while tolerating a rise in $PaCO_2$. This represents one of the most significant single advances in CDH care in recent years [10].

CDH is no longer believed to require immediate surgery, since the primary problem after birth is not the herniation of abdominal viscera into the chest but rather severe pulmonary hypoplasia associated with pulmonary hypertension [1]. As a result, most centers practice delayed surgical repair of CDH following a period of preoperative stabilization [13,14]. Our data clearly demonstrate this approach by deferring surgery, as was done in group 2 [Table 2].

None of our patients had intrauterine treatment (tracheal ligation or ballooning) for the lesion [15]. Post-delivery surgery was planned based on evaluating the infant's hemodynamic and pulmonary profile. Our surgical policy supports the trend that surgery should be delayed until there has been a reduction in pulmonary vascular resistance and ventilation can be maintained as low as possible for peak inspiratory pressure and oxygen requirements [16]. In our institute, we follow a multidisciplinary team approach that involves neonatologists, pediatric surgeons, a cardiologist and a radiologist.

The overall and the post-surgery mortality for the group 2 cases with CDH is lower in our series (28.8% and 13.5% respectively) compared to that reported in the international literature [3,4]. This finding may be explained by several factors. First, in Israel prenatal ultrasound has been established as a general practice and is almost universally performed [17]. These frequent prenatal ultrasound examinations have been shown to affect the rate of congenital anomalies detected prior to birth. This in turn affects the incidence of pregnancies terminated for selected anomalies and, as a consequence, the prevalence of anomalies in live-born infants [18]. This is likely to be the case in CDH cases in Israel, as reflected in our data. Earlier detection and the detection of coexistence of other malformations (e.g., cardiac malformations) create a selection bias towards termination of pregnancy for cases of CDH with a poor prognosis. As a result the cases that are born are probably those with a better chance for survival. Prenatal mortality (known also as "hidden mortality") should also be mentioned since spontaneous abortions are common in fetuses with diaphragmatic hernia, but its prevalence was not available for the present study.

Another important impact of early CDH detection is the fact that it gives health care providers time to prepare for proper delivery. This involves choosing the appropriate hospital for the delivery and preparing for the delivery by making available critically important life-saving procedures for infants with CDH (intubation and ventilation), which must be performed immediately after birth.

In analyzing the positive predictors for survival in group 2 [Table 3], we found that the need for aggressive preoperative mechanical ventilation is clearly related to higher mortality. This fact can be interpreted in two ways. Higher ventilation parameters probably reflect ventilation difficulties due to lung injury or underdevelopment, a factor that is clearly related to mortality. On the other hand, aggressive ventilation parameters can be an independent contributing factor for mortality. Furthermore, in our experience in most of the cases where we failed to maintain mechanical ventilation and turned to extracorporeal membrane oxygenation as a rescue mode, the death rate was high.

Conclusions

CDH is a challenging medical situation for which a prompt post-delivery multidisciplinary treatment approach should be taken. Prenatal diagnosis as well as planned delivery and modern treatment policies have improved the survival of infants with CDH and other co-morbidities. Improved survival over the last decade is a result of improved preoperative medical treatment and relatively late surgery timing compared to the past. In addition, today

HFV = high frequency ventilation

we probably deal with milder forms of CDH, due to earlier and more detailed prenatal diagnosis and subsequent termination of pregnancies for the more severe forms.

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