

Congenital Diaphragmatic Hernia: Short-Term Outcome

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ABSTRACT: **Background:** Despite progress in medical and surgical care the mortality rate of congenital diaphragmatic hernia remains high. Assessment of short-term outcome is important for comparison between different medical centers.

Objectives: To evaluate the short-term outcome of infants born with symptomatic CDH and to correlate demographic and clinical parameters with short-term outcome.

Methods: We performed a retrospective cohort study in which demographic, obstetric and perinatal characteristics were extracted from infants' files. For comparison of categorical variables chi-square test and Fisher's exact test were used and for comparison of continuous variables with categorical variables the Mann-Whitney test was used. Sensitivity and specificity were estimated by receiver operator curve.

Results: The study group comprised 54 infants with CDH, of whom 20 (37%) survived the neonatal period. Demographic characteristics were not associated with survival. Regarding antenatal characteristics, absence of polyhydramnion and postnatal diagnosis were correlated with better survival. Apgar scores (above 5 at 1 minute and 7 at 5 minutes), first arterial pH after delivery (above 7.135) and presence of pulmonary hypertension were significantly correlated with survival. Also, infants surviving up to 6 days were 10.71 times more likely to survive the neonatal period.

Conclusions: The survival rate of symptomatic newborns with CDH at our center was 37% for the period 1988–2006. Prenatal diagnosis, Apgar score at 5 minutes and first pH after delivery were found to be the most significant predictors of survival. Prospective work is needed to evaluate the long-term outcome of infants with CDH.

IMAJ 2009;11:219–224

KEY WORDS: congenital diaphragmatic hernia, outcome, neonate, prenatal diagnosis, Apgar score

the mortality rate remains high (40–80%) [2]. Over the past 30 years CDH has been recognized as a syndrome, which includes pulmonary hypoplasia, lung immaturity, left heart hypoplasia and persistent pulmonary hypertension of the newborn. The severity of CDH is variable: from well-tolerated CDH, diagnosed only after the neonatal period, to cases of severe respiratory and hemodynamic failure within the first 6 hours of life. The severity of CDH is probably related to the timing and degree of prenatal visceral herniation. The prognosis of infants with CDH depends on the extent of pulmonary hypoplasia [3] and associated congenital malformations [4].

The low survival rates prompted clinicians to seek novel treatment strategies and predictors of outcome. For example, antenatal diagnosis before 25 weeks gestational age [5], associated malformations [6] and intrathoracic position of the stomach [7] were found to be predictors of poor outcome.

Soroka Medical Center is the only referral center for southern Israel and serves a population of more than 500,000. The delivery rate is around 12,000 live births annually. Infants with CDH have been treated in the center since 1975. The center does not have an ECMO (extracorporeal membrane oxygenation) facility. Assessment of short-term outcome is important for comparison of our medical center with other facilities, feedback to the clinicians, and for the accumulation of data for the long-term evaluation of these infants.

The primary objective of our study was to evaluate the short-term outcome of infants who were diagnosed with CDH soon after birth and treated in the early neonatal period at Soroka. The secondary goal was to correlate demographic and clinical parameters before and soon after birth with the short-term outcome of these infants.

PATIENTS AND METHODS

We conducted a retrospective cohort study of infants with CDH who were born at Soroka Medical Center between 1988 and 2006. Infants with diaphragmatic eventration or any diaphragmatic defect other than CDH were excluded from the study. Infants and children diagnosed after the neonatal period were dealt with separately. The study was approved by the local institutional ethics committee.

Congenital diaphragmatic hernia was first described in the early 18th century by Bochdalek and was considered as a hole in the diaphragm [1]. However, despite progress in medical and surgical care, its pathogenesis is still unclear and

*This work was part of the MD thesis of Shlomo Cohen-Katan
CDH = congenital diaphragmatic hernia

Table 1. Demographic and antenatal characteristics of congenital diaphragmatic hernia cases in Soroka Medical Center and their relation to survival, 1988–2006 (N=54)

| | Survivors (N=20) | Non-survivors (N=34) | P |
|--------------------------------|------------------|----------------------|-------|
| Gender | | | |
| Male | 12 (37.5) | 20 (62.5) | 0.932 |
| Female | 8 (36) | 14 (64) | |
| Ethnic group | | | |
| Bedouin | 12 (36) | 21 (64) | 0.898 |
| Jewish | 8 (38) | 13 (62) | |
| Year of birth | | | |
| 1988-1991 | 0 (0) | 7 (100) | 0.038 |
| 1992-2006 | 20 (43) | 27 (57) | |
| Diagnosis (N=53) | | | |
| Prenatal | 4 (15) | 23 (85) | 0.001 |
| Postnatal** | 15 (58) | 11 (42) | |
| Polyhydramnion (N=45) | | | |
| Present | 1 (8) | 12 (92) | 0.013 |
| Absent | 15 (47) | 17 (53) | |
| Hospital of birth | | | |
| Inborn | 17 (41) | 34 (59) | 0.046 |
| Outborn | 3 (100) | 0 (0) | |
| Mode of delivery (N=53) | | | |
| Vaginal/ Assisted | 17 (40) | 25 (60) | 0.17 |
| Cesarean section | 2 (18) | 9 (82) | |

Values are as presented No. (%)

* Chi-square test / Fisher's exact test

** Two cases with no prenatal care were included.

Table 2. Perinatal characteristics vs. survival in CDH cases, 1988–2006 (N=54)

| | Survivors (N=20) | Non-survivors (N=34) | P |
|---|------------------------|-----------------------|----------|
| Side of hernia (N=52) | | | |
| Left | 16 (44) | 20 (56) | 0.076§ |
| Right | 3 (18.75) | 13 (81.25) | |
| Gestational age at birth (wks) | 39 (33–43) | 39 (27–43) | 0.739§§ |
| Umbilical cord pH* | 7.312 (7.04–7.38) | 7.279 (7.00–7.41) | 0.122§§ |
| First pH after delivery* | 7.200 (7.00–7.36) | 7.110 (6.48–7.28) | 0.003§§ |
| 1 min Apgar score* | 9 (4–0, 5–9) | 4 (1–9, 1–7) | <0.001§§ |
| 5 min Apgar score* | 10 (5–10, 8–10) | 6 (0–9, 2–7) | <0.001§§ |
| Pneumothorax (N=53) | | | |
| Present | 0 (0) | 4 (100) | 0.285§ |
| Absent | 20 (29) | 29 (71) | |
| Pulmonary hypertension** | | | |
| Present | 8 (29) | 20 (71) | 0.044§ |
| Absent | 11 (58) | 8 (42) | |
| Weight at birth (g) | 2990.0 (2205.0–3815.0) | 2742.5 (745.0–4614.0) | 0.078§§ |
| Head circumference at birth (cm) | 33.75 (31.5–37.0) | 33.5 (28.0–56.0) | 0.495§§ |
| Other anomalies | | | |
| Present | 6 (50) | 6 (50) | 0.292§ |
| Absent | 14 (33.33) | 28 (66.67) | |

Values are presented as No. (%) and

* Data presented as median (minimum to maximum)

** N=47 (Missing data due to infants without echocardiography prior to surgery)

§ Chi-square test / Fisher's exact test

§§ Mann-Whitney test for independent samples

Cases were retrieved from three different databases: the Soroka archive, the neonatal intensive care unit discharge summary log book, and the pediatric surgical department surgery books. The files of infants and their mothers who met the inclusion criteria were retrieved from the medical center archive (infants whose files could not be retrieved from the archives were excluded since their diagnosis could not be confirmed). The following data were extracted: demographic characteristics, timing of detection of the hernia (gestational week of detection if prenatal or postnatal), presence of poly/oligohydramnios prenatally, method of delivery and obstetric complications; gestational age at birth, birth weight, head circumference, need for resuscitation at delivery, Apgar scores, umbilical cord pH and first arterial pH after delivery, presence of associated anomalies, age at surgery (if done), type of surgical repair, contents and location of hernia; acute postoperative complications; use, type and duration of assisted ventilation; use of pharmacological treatment – namely, surfactant, pulmonary vasodilators: epoprostenol sodium (prostacyclin), nitric oxide, tolazoline and inotropic agents (dopamine, dobutamine, adrenaline); time to enteral nutrition, time of oxygen requirement, duration of hospital stay or age at death.

Data were analyzed using SPSS for Windows (version 14) software. For comparison of categorical variables chi-square test and Fisher's exact test were used. For comparison of continuous variables with categorical variables the non-parametric test, Mann-Whitney for independent samples, was used. Sensitivity and specificity were estimated by ROC (receiver operator curve). Variables found to be significantly correlated to survival were further analyzed through a logistic regression model.

RESULTS

Ninety-eight cases were considered for inclusion on the basis of the different sources. Eight files could not be retrieved for ascertainment of the diagnosis, 25 did not have a diagnosis of CDH. The files of 65 infants diagnosed with CDH were retrieved, of whom 54 were diagnosed in the neonatal period; 20 (37%) survived the neonatal period; 11 were diagnosed in the post-neonatal period (age at surgery: median 10.5 months, range 50 days to 16 years old), of whom 9 (81.82%) survived.

Demographic characteristics [Table 1] were not associated with survival. Considering the year of birth, none of the seven infants diagnosed with CDH between 1988 and 1991 survived whereas 20 (43%) infants born between 1992 and 2006 did ($P = 0.038$). Of the antenatal characteristics, absence of polyhydramnion (47% vs. 8% with polyhydramnion) and postnatal diagnosis (58% vs. 15% with prenatal diagnosis) were correlated to better survival.

Table 3. Antenatal and postnatal treatment vs. survival in CDH cases (1988–2006) (N=54)

| | Survivors (N=20) | Non-survivors (N=34) | P |
|--|------------------|----------------------|--------|
| Prenatal steroid (N=53) | | | |
| Given | 0 (0) | 4 (100) | 0.284§ |
| Not given | 19 (39) | 30 (61) | |
| Surfactant (N=52) | | | |
| Given | 6 (23) | 20 (67) | 0.08§ |
| Not given | 12 (46) | 14 (54) | |
| Ventilation (N=47) | | | |
| Conventional | 8 (50) | 8 (50) | .097§ |
| Conventional & high frequency | 8 (26) | 23 (74) | |
| No. of drugs (N=50) | | | |
| ≤1 drug | 10 (59) | 7 (41) | 0.029§ |
| > 1 drug | 9 (27) | 24 (73) | |
| Pulmonary vasodilators (N=52)[^] | | | |
| Given | 7 (23) | 23 (77) | 0.021§ |
| Not given | 12 (55) | 10 (45) | |
| NaHCO₃ (N=53) | | | |
| Given | 8 (35) | 15 (65) | 0.698§ |
| Not given | 12 (40) | 18 (60) | |
| Inotropic agents (N=53)[*] | | | |
| Given | 9 (28) | 23 (72) | 0.075§ |
| Not given | 11 (52) | 10 (48) | |
| Paralyzing agents^{**} | | | |
| Given | 10 (29) | 25 (71) | 0.08§ |
| Not given | 10 (53) | 9 (47) | |
| Preoperative thoracal drain | | | |
| Given | 0 (0) | 6 (100) | 0.074§ |
| Not given | 20 (42) | 28 (58) | |

§ Chi-square test / Fisher's exact test

[^]Pulmonary vasodilators: Flolan/ NO/ Tolazoline

^{*}Inotropic agents: Dopamine/ Dobutamine/ Adrenaline

^{**}Paralyzing agents: Pavulon/ Norcuron

CLINICAL CHARACTERISTICS [TABLE 2]

Apgar scores (1 and 5 minutes), the first arterial pH after delivery, and presence of pulmonary hypertension were significantly correlated with survival. Using ROC statistics, the cutoff value for 1 minute Apgar was 5.5 (sensitivity 73%, specificity 67%, $P < 0.001$), for 5 minute Apgar 7.5 (sensitivity 80%, specificity 67%, $P < 0.001$), and for first pH after delivery 7.135 (sensitivity 72%, specificity 68%, $P = 0.003$).

Infants who survived up to 6 days (irrespective of the time of surgery) had 10.71 times more chances to survive the neonatal period than infants who did not reach their sixth day of life ($P = 0.002$). Using ROC statistics a cutoff of 8.5 days was computed (sensitivity 77%, specificity 65%, $P = 0.015$).

ANTENATAL AND POSTNATAL TREATMENT [TABLE 3]

Use of more than one drug was associated with higher mortality ($P = 0.029$). Considering drug groups only, the administration of pulmonary vasodilators was correlated to higher mortality rate.

ROC = receiver operator curve

Table 4. Surgical characteristics vs. survival in CDH cases, 1988–2006 (N=54)

| | Survivors (N=20) | Non-survivors (N=34) | P |
|---|------------------|----------------------|----------|
| Surgery | | | |
| Performed | 20 (67) | 10 (33) | < 0.001* |
| Not performed | 0 | 24 (100) | |
| Closure type (N=28) | | | |
| Primary | 19 (79) | 5 (21) | 0.058* |
| Patch | 1 (25) | 3 (75) | |
| Duration (N=25) | | | |
| ≤ 3 hours | 18 (86) | 3 (14) | 0.031* |
| > 3 hours | 1 (25) | 3 (75) | |
| Age at surgery (days)^{***} | 2 (0–82) | 5.5 (1–24) | 0.150** |
| No. of organs in chest cavity (N=36) | | | |
| 1 organ | 0 (0) | 6 (100) | 0.006* |
| > 1 organ | 19 (63) | 11 (37) | |
| Small bowel (N=35) | | | |
| Present | 18 (64) | (36) 10 | 0.032* |
| Absent | 1 (14) | (86) 6 | |
| Large bowel (N=35) | | | |
| Present | 16 (76) | 5 (24) | 0.002* |
| Absent | 3 (7) | 11 (93) | |
| Spleen (left side hernia) (N=32) | | | |
| Present | 13 (72) | 5 (28) | 0.011* |
| Absent | 3 (21) | 11 (79) | |
| Liver (right side hernia) (N=14) | | | |
| Present | 3 (25) | 9 (75) | 1* |
| Absent | (0) 0 | 2 (100) | |
| Stomach (left side hernia)^o | | | |
| Present | 8 (42) | 11 (58) | 0.280* |
| Absent | 8 (62) | 5 (38) | |
| Kidney | | | |
| Present | 4 (100) | 0 (0) | 0.027* |
| Absent | 16 (37) | 27 (63) | |

* Chi-square test / Fisher's exact test

** Mann-Whitney test for independent samples

*** Data presented as median (minimum to maximum)

SURGICAL CHARACTERISTICS [TABLE 4]

Surgery lasting more than 3 hours and the presence of only one organ in the chest cavity were associated with higher mortality rate. Chest content was verified during surgery or by radiography in cases where infants were not operated (postmortem examinations are seldom performed in our center for cultural and religious reasons). Presence of bowel, spleen or kidney in the chest cavity was associated with lower mortality rate.

Congenital anomalies were present in 12 cases (22.22%) and yielded a 50% survival rate ($P = 0.292$). These anomalies were musculoskeletal (n=1), cardiovascular (ventricular septal defect or atrioventricular canal) (n=4), central nervous system (hydrocephalus) (n=1), gastrointestinal (n=4) and craniofacial (n=3).

The three most significant parameters in univariate analysis – 5 minute Apgar, prenatal diagnosis and first pH after delivery – were included in a logistic regression model that

yielded only prenatal diagnosis (odds ratio 0.05, 95% confidence interval: 0.04–0.6, $P = 0.019$) and 5 minute Apgar ≤ 7 (OR 3.067, 95% CI 1.3–7.1, $P = 0.009$) as significant predictors for survival. Of note is that none of the infants who were diagnosed prenatally and scored less than 8 at 5 minutes survived the neonatal period (14 cases). The combination of these two variables as a single variable predicted mortality with a sensitivity of 94% and specificity of 80% ($P = 0.003$)

DISCUSSION

The study group comprised 54 cases of symptomatic CDH. The overall mortality rate was 63%. The following early clinical parameters were significantly correlated with mortality: prenatal diagnosis, first pH after delivery of less than 7.135, Apgar score less than 6 at 1 minute and less than 8 at 5 minutes. Other parameters found to correlate with mortality were the year of birth, polyhydramnion, pulmonary hypertension, and duration of surgery. Of the babies who survived the neonatal period 95.24% (20/21) were alive at the time this report was written.

Soroka Medical Center is the only referral center in southern Israel with level three neonatal intensive care and neonatal surgical capabilities. Three infants in this cohort were referred to our center from another hospital (and survived after surgery), but there may have been cases diagnosed in our catchment area who opted to deliver in another medical center. We believe that our data retrieval method traced nearly all the infants with CDH who were treated in the immediate neonatal period; therefore, a mortality rate of 63% is an accurate estimate for liveborn infants with CDH in southern Israel. However, we may have under-diagnosed the true mortality rate since we were unable to retrieve data on the rate of termination of pregnancy due to a prenatal diagnosis of CDH and according to the present findings and others [5] this group of infants has a higher mortality rate. This discrepancy was coined "hidden mortality" by Harrison et al. [8] who referred to the death of infants with CDH before their arrival at a referral center. Additionally, to ascertain the true incidence and mortality of CDH, autopsies of stillbirths, pregnancy termination and neonatal deaths were taken into account. Of interest is the report by Colvin et al. [9] where 35% of all live-born infants with CDH died before referral or transport and 13% of all CDH cases were diagnosed in post-mortem examinations of products of pregnancy termination and peripartum deaths.

Some studies demonstrated that right-sided hernia is associated with higher mortality [8,10]. In our cohort the difference was nearly significant with a mortality rate of 81.25% in infants with right CDH as compared to 56% in left CDH.

The definitive treatment in CDH is surgery. Throughout the study period, a policy of delayed surgery after preoperative stabilization of the infant was practiced. Two-thirds of post-operative infants (20 of 30) survived (including outborn); that rate is slightly lower than the result of Clark et al. [11] who studied the surgical characteristics of CDH and found a 75% survival rate among 373 infants who underwent corrective surgery, and identical to that in the cohort of Harmath and collaborators [12]. The median age of hernia repair reported in two contemporary studies was 24 hours to 4 days [9,11]; in our cohort it was 2 days. Duration of the surgical procedure itself was found to be correlated to survival, with over 3 hours being correlated with higher mortality (though it lasted longer than 3 hours in only four infants, three of whom died); this correlation was not reported by other authors.

With regard to the contents of organs in the chest cavity, a correlation of the presence of the spleen in the chest cavity with higher survival was also reported by Harmath et al. [12]. The correlation of decreased mortality with more than one organ in the chest cavity or decreased mortality with the presence of kidney or bowel has not been reported elsewhere. The difference in mortality rate that we found between infants with the liver present or absent in the thoracic cavity (72% and 54% respectively) was not statistically significant as compared to other reports [12]. The presence of stomach was not correlated with higher mortality in our cohort as compared to others [7,12].

In our cohort 51% of the cases were diagnosed prenatally. The prenatal detection rate for CDH varies enormously in published studies, from 10% [13] to 79% [14], reflecting differences in local protocols of prenatal care and variable sonographic expertise. In our area, ultrasonographic system scan is offered at the end of the second trimester but due to religious and cultural issues, not all mothers take advantage of this offer.

We did not find any association between the gestational age at diagnosis and survival. The literature on this topic is conflicting, with some studies reporting increased mortality rates for infants diagnosed earlier [5] and others failing to find such an association [10,15]. Many prenatal sonographic predictors of outcome have been proposed, including polyhydramnion [10], intrathoracic stomach [10], abdominal circumference [16], and major mediastinal shift [10]. In our cohort polyhydramnion was associated with increased mortality rates, but unfortunately we could not retrieve information on other prenatal ultrasonographic variables.

Prenatal diagnosis itself was found to have a strong association with mortality of live-born infants in our cohort – a survival rate of 14.8% versus 57.69% for postnatally diagnosed infants (OR 7.84). Prenatal diagnosis was found in many studies to be associated with increased mortality rates [9,10,14,17-19], although it is not a universal finding [14,20]. It is possible that prenatal diagnosis detects cases with a greater degree or longer duration of visceral herniation and

OR = odds ratio
CI = confidence interval

thus an increased severity of pulmonary hypoplasia.

Other studies demonstrated that gestational age at birth [15] especially early gestational age at birth (preterm delivery) [9], birth weight [5,8,13], Apgar scores [13,15,18] and pneumothorax [18,19] are predictive of mortality rates in CDH. In our cohort, gestational age, pneumothorax and type of delivery were not correlated to mortality. Apgar scores at 1 and 5 minutes were found to be significantly correlated.

Few studies checked the blood pH correlation to survival. In one [21] no correlation was found while in another [20] a cutoff value of 7.25 was found on receiver operating curve statistics with a sensitivity of 55% and specificity of 87% and a non-significant *P* value when comparing survivors to non-survivors, while in our cohort the cutoff value by ROC statistics of the first arterial pH (arterial blood gases are routinely taken immediately after the insertion of an umbilical arterial line) was 7.135 with a sensitivity of 72% and specificity of 68% and *P* < 0.003.

MORTALITY RATES

The overall mortality rate of 63% in this cohort is on the higher border of mortality rates reported in other population-based studies (37%–69%) [2,9,11,17]. Many institutions have reported significant improvements in the survival rates for neonates with CDH in the past decade [12,22]. Others also found constant mortality rates over the past 30 years, ranging from 66% in the 1970s [8] to 62% in the 1990s [17]. Therefore, although specific subgroups of infants may show improved survival rates compared with their predecessors, the overall mortality rate for this condition remains static [9]. In the present study we found a difference between the group of infants born before 1992 (100% death rate) and those born after 1992 (57% death rate). This kind of difference between epochs can be caused by a change in approach to CDH or more advanced equipment, which is not the case in our cohort since already in 1992 delayed treatment was practiced and high frequency ventilation and nitric oxide were available. This difference could be due to chance alone.

ADDITIONAL MAJOR ANOMALIES

In most reported cohorts [10,15,17,23], but not all [18], additional major congenital anomalies were associated with a decreased survival rate. The proportion of infants with coexisting major anomalies among live-born infants in our study population was 22%, a low rate compared to other population-based studies, namely 37–47% [17,24]. An even larger actual incidence of major malformations (72%) was reported [9], when cases of pregnancy termination and postmortem examinations of most of the pregnancy products are taken into account [23]. Furthermore, these additional anomalies were not life threatening, a finding that could explain why their presence was not correlated to higher mortality rates.

This study has shortcomings, mainly its retrospective

nature. We tried to trace most infants and children with CDH born or treated in our center. We believe that by using three independent databases nearly all of these infants were traced. The most complete database is the neonatal intensive care unit where all the discharge summaries are kept. Of the eight files that could not be retrieved only one discharge summary was found in the NICU database of an infant who was diagnosed with trisomy 18. Since his file could not be retrieved from the hospital archive he was not included in this report.

We also were not able to reliably retrieve data from the files for calculation of oxygenation indices and other formulas that were used for prediction of survival [25]; therefore, we focused on more simple clinical criteria.

Another shortcoming is the size of the cohort, which was not large enough to draw more definitive conclusions on some topics that were found to be of borderline statistical significance, for example, the correlation of survival and the hernia side, weight at birth, type of closure, preoperative drainage, use of surfactant, paralyzing agents and inotropic agents, but retrieving data before 1988 would have created other problems in data processing due to different treatment modalities and lower yield of data from the different sources.

CONCLUSIONS

The survival rate at Soroka University Medical Center of symptomatic infants with CDH is 37% for the period 1988–2006 and 43% from 1992 to 2006. For those infants who reached surgery the survival rate was 67%. In univariate analysis, the prenatal diagnosis, Apgar score at 5 minutes and first pH after delivery were found to be the most significant predictors of mortality while only prenatal diagnosis and Apgar score at 5 minutes remained significant on multivariate analysis. More prospective work is needed for the evaluation of long-term outcome of infants with CDH in view of reports of a high rate of respiratory, motor and language problems in early childhood.

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NICU = neonatal intensive care unit

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