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Perinatal Factors Associated with Poor Neurocognitive Outcome in Early School Age Congenital Diaphragmatic Hernia Survivors

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Abstract

Objective—Determine predictors of neurocognitive outcome in early school age congenital diaphragmatic hernia (CDH) survivors.

Study design—Prospective study of infants with CDH at Duke University Medical Center. Neurocognitive delay (NCD) at school age (4 to 7 years) was defined as a score < 80 in any of the following areas: Verbal Scale IQ, Performance Scale IQ, Expressive Language, or Receptive Language. Logistic regression, Fisher's exact, and the Wilcoxon rank sum test were used to examine the relationship between NCD at early school age and 6 demographic and 18 medical variables.

Results—Of 43 infants with CDH, twenty seven (63%) survived to hospital discharge, and 16 (59%) returned for school age testing at a median age of 4.9 years. Seven (44%) of the children evaluated had NCD. Patch repair ($p=0.01$), extracorporeal membrane oxygenation (ECMO; $p=0.02$), days on ECMO ($p=0.01$), days of mechanical ventilation ($p=0.049$), and post-operative use of inhaled nitric oxide ($p=0.02$) were found to be associated with NCD at early school age.

Conclusions—CDH survivors are at risk for neurocognitive delay persisting into school age. Perinatal factors such as patch repair and ECMO treatment may aid in identifying CDH survivors at high risk for continued learning difficulties throughout childhood.

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RFG jointly conceived the study, supervised all aspects of the project, and contributed to manuscript revision.

All authors discussed the results and implications and commented on the manuscript at all stages.

Keywords

hernia, diaphragmatic; follow-up studies; neurobehavioral manifestations; growth & development; infant nutrition disorders

Introduction

Congenital diaphragmatic hernia (CDH) occurs in approximately 1 in 3000-5000 live births,^[1-3] with overall mortality ranging between 40-70% despite continuing advances in prenatal diagnosis and postnatal management.^[4-10] CDH survivors experience predictable pulmonary, gastrointestinal, cardiac, and neurologic morbidities,^[11-14] including growth and nutrition difficulties, feeding problems, symptomatic gastroesophageal reflux (GER), and failure to thrive.^[15-17] Survivors are more likely to have chronic lung disease, bronchial hyperreactivity, and persistent pulmonary hypertension.^[18, 19] A significant number show evidence of neurocognitive delay (NCD), hearing impairment, and behavioral disorders at follow-up.^[20-23]

Most outcome studies of CDH survivors have focused on 18-36 month follow-up.^[13, 14, 23, 24] Although some recent reports examine the developmental and psychological outcomes of CDH survivors into late childhood and adolescence,^[20, 22] identification of perinatal and postnatal factors that may be predictive of persistent cognitive or developmental delays is lacking. Understanding which patients with CDH are likely to experience long-term neurodevelopmental impairment may help guide treatment strategies in the NICU and allow better evaluation of management protocols. Further, a predictive model may help parents make informed decisions about aggressiveness of care while enabling medical providers to optimize outcomes for this unique – and highly complex – group of patients.

Methods

Subjects

We identified all infants with CDH diagnosed prenatally or within the first 24 hours of life who were treated at Duke University Medical Center between 2001 and 2005. In order to avoid bias in our statistical calculations, we included in our analysis those infants who were born with CDH but did not survive. During the study period, infants with CDH were treated according to a specific CDH management protocol designed to minimize lung injury with early use of high frequency jet ventilation, iNO, and selective and early utilization of ECMO support.^[25] ECMO was performed via venoarterial access and used as a rescue strategy after failure of medical management to prevent the development of irreversible heart failure in infants with severe pulmonary hypertension and poor cardiac function. During the study time period, two pediatric surgeons operated on infants with CDH, and the relative number of cases were approximately equal among the surgeons. Both pediatric surgeons had considerable experience with repair of CDH. All CDH survivors 4 years old at the time of study enrollment were eligible. Given the lack of reliable neurodevelopmental outcome measures for non-English speakers, children with a primary language other than English were excluded. The study was approved by the Institutional Review Board, and informed parental consent was obtained.

Assessment procedures

Perinatal, perioperative, and post-discharge data were recorded for all 43 infants in the cohort. All eligible subjects were invited to participate in the school age medical and

neurodevelopmental evaluation. A detailed medical history, physical examination, and neurologic examination were performed for all subjects by a single examiner. Parents completed questionnaires about education levels, socioeconomic status, and their child's degree of asthma symptoms. Growth parameters including weight, height, head circumference, and body mass index (BMI) were measured and plotted on standard reference curves. Oxygen saturation was measured in room air. Chest radiography and pulmonary function testing using pre- and post-bronchodilator spirometry were performed. Echocardiography was performed for subjects with evidence of pulmonary hypertension on their most recent echocardiogram.

Cognitive assessment was performed using the Wechsler Preschool and Primary Scale of Intelligence – Third Edition (WPPSI-III). The WPPSI-III is an individually administered clinical assessment tool for evaluating the cognitive functioning of children age 2 years, 6 months through 7 years, 3 months. It is widely considered the gold standard assessment tool for preschool and early elementary aged children. The WPPSI-III assesses a range of cognitive abilities including verbal abilities, such as reasoning, comprehension, and conceptualization, as well as nonverbal abilities, such as perceptual reasoning and visual-spatial analysis. This instrument yields a Full Scale IQ (FIQ), Verbal Scale IQ (VIQ), Performance Scale IQ (PIQ), and Processing Speed Index. Each of the composite scores has a mean of 100 and a standard deviation of 15. Scores may range between 40 and 160 with Average scores falling between 90 and 110.

Language assessment was performed using the Test of Early Language Development - Third Edition (TELD-3), a measure of spoken language abilities for children aged 2 years, 0 months through 7 years, 11 months. The TELD-3 yields subscores for both Receptive Language (meaningful listening and auditory comprehension) and Expressive Language (ability to construct and produce meaningful oral responses), as well as for the overall composite Spoken Language score. Each of these three scores has a mean of 100 and a standard deviation of 15. Scores may range between 50 and 150 with Average scores falling between 90 and 110.

All cognitive and language assessment measures were administered by a licensed pediatric clinical psychologist or supervised pre-doctoral psychology trainees. Standardized administration and scoring procedures as detailed in the published assessment manuals were used.

Definition of NCD

In order to capture the majority of subjects who would be expected to experience some degree of difficulty in a typical classroom, NCD was defined by a composite standard score < 80 in any of the following areas: Verbal Scale IQ, Performance Scale IQ, Expressive Language, or Receptive Language. Subjects with scores in this range were functioning at less than the 10th percentile, indicating that more than 90 percent of age-mates demonstrate higher functioning. Thus, these subjects demonstrated evidence of at least mild delay in at least one neurocognitive domain.

Statistical methods

Fisher's exact test or Wilcoxon rank sum test were used where appropriate to examine the relationship between NCD at early school age and 6 demographic and 18 medical variables. Univariable logistic regression analysis was used to predict death or NCD based on need for ECMO, patch repair, and duration of mechanical ventilation. A two-tailed p value < 0.05 was considered to be statistically significant. Statistical testing was performed using STATA 10 (College Station, TX).

Results

Of the 43 infants with CDH, 27 (63%) survived to hospital discharge. Three of the 27 survivors were excluded from the follow-up portion of the study because of a lack of proficiency in English (all were Spanish-speaking). Despite attempts to locate families of all eligible survivors, 7 were deemed lost to follow-up. The remaining 16 subjects were enrolled in this pilot study (Figure 1).

There were no differences in demographic, perinatal, and postnatal factors between the enrolled subjects compared to the 11 who were eligible but not enrolled. The 16 enrolled subjects had a median birth weight and gestational age of 3293 grams (range; 2560, 4445) and 39 weeks (34, 41), respectively. Nine (56%) were inborn, and 9 (56%) had a left-sided diaphragmatic defect. Two subjects had congenital heart disease; one with a ventricular septal defect, and the other with aortic arch hypoplasia and aortic valve stenosis. Seven infants (44%) required patch repair of the diaphragm. Four infants (25%) were treated with ECMO in the neonatal period, and spent a median of 15 days on ECMO. Nearly 50% of enrolled subjects were treated with inhaled nitric oxide (iNO) prior to repair, but only 25% received iNO post-operatively. (Table 1)

The median age at early school age follow-up was 4.9 years (range: 4.3, 7.5). Seven survivors (44%) met criteria for NCD at school age, while 9 (56%) did not. The demographic and physiologic characteristics of the subjects with and without NCD were similar between the two groups. Patch repair ($p=0.009$), treatment with ECMO ($p=0.019$), duration of mechanical ventilation ($p=0.049$), time spent on ECMO ($p=0.01$), and use of post-operative iNO ($p=0.019$) were significantly different between the two groups, and predictive of continued NCD at early school age. None of the subjects who survived without impairment were treated with ECMO or post-operative iNO in the neonatal period. (Table 2) Univariate logistic regression was performed to identify associations between predictive variables and NCD. Patch repair was associated with continued neurocognitive impairment at early school age, odds ratio (OR) = 48 [95% confidence interval; 2.4, 933], $p=0.01$. ECMO ($p=0.02$), ECMO duration ($p=0.01$), and post-operative use of iNO ($p=0.02$) were also predictive of continued NCD at school age. As birth weight increased, there was a trend toward a decreased risk for NCD although this was not statistically significant. Prolonged mechanical ventilation, OR=1.15 [0.99, 1.36], $p=0.07$, and pre-operative use of iNO, OR=8.8 [0.90, 84.8], $p=0.06$, showed a trend toward statistical significance. Abnormal findings on neuroimaging studies were not predictive of NCD at school age, $p=0.99$. Note that odds ratios are not applicable to all factors as there were some infants who did not require ECMO treatment or post-operative iNO.

Although the overall median FIQ for enrolled subjects was 89, the median FIQ for subjects without NCD was 99 (range 87, 121) compared to 81 for those with NCD (58, 84), $p=0.0008$. Similarly, the median VIQ for subjects without NCD was 96 (81, 127) versus 80 (67, 93) for those with NCD, $p=0.003$. Additional scores for the cognitive (WPPSI) and language (TELD) testing components are detailed in the table. (Table 3)

Of the 16 CDH survivors seen at early school age, 8 (50%) were also seen at 2 years of age for developmental testing using the Bayley Scales of Infant Development, version II.^[26] Four subjects (50%) had mental development index scores < 70 at 2-year testing, consistent with a diagnosis of neurodevelopmental impairment. Notably, all four of these children were treated with ECMO in the neonatal period, and three had abnormalities on brain imaging obtained within the first two months of life as follows: evidence of chronic infarction and encephalomalacia (1), hydrocephalus ex vacuo (1), and cystic encephalomalacia (1). The

same four children with early impairment had NCD at early school age, while the subjects who scored within the average range at 2 years remained with average scores at school age.

The median resting oxygen saturation of enrolled subjects was 97% (94, 99). The median BMI of enrolled subjects was 15.4 (12.7, 17.5). There was no significant association between BMI and NCD at early school age, $p=0.43$. Three of 16 children (19%) had abnormal findings on chest radiography, but 83% of the 12 subjects who underwent pulmonary function testing had evidence of restrictive lung disease. All six echocardiographic studies were normal except for one showing moderate right ventricular enlargement. According to parental report, 6 children (38%) had persistent growth difficulties, 9 (56%) had ongoing respiratory problems, and 4 (25%) had continued learning difficulties.

The socioeconomic data for the enrolled subjects' primary caretakers is as follows: 47% of the subjects' mothers received a high school diploma or GED as their highest education level completed. Forty percent of mothers attended college for some period of time or received an Associate's Degree, and 14% percent completed either a Bachelor's Degree or a Doctorate or Professional degree. Paternal education level was not reported for all subjects, but 33% received a high school diploma or GED, 33% attended partial college, and 33% earned a Bachelor's Degree or Master's Degree. Ninety-four percent of subjects had at least one parent employed outside of the home, and 79% were employed full-time. Total income levels ranged between < \$10K and \$125-\$200K, with 69% of families earning between \$10-50K per year. English was reported as the primary language in 87% of homes.

Discussion

This study provides an examination of early school age outcomes in a cohort of CDH survivors and highlights the importance of continued long term follow-up by medical and developmental experts, as close to one half of CDH survivors demonstrated evidence of persistent delays into early childhood. Our findings confirm the results of previous studies showing CDH infants who have a large diaphragmatic defect requiring patch repair, undergo a prolonged duration of mechanical ventilation, and need ECMO support in the perioperative period are at high risk for significant neurocognitive impairment.^[27-29]

The need to use ECMO in the CDH population has been associated with significant long-term morbidity.^[30] Davis *et al* found 19% of ECMO-treated CDH survivors had severe neurodevelopmental problems (defined as speech, language, or motor delay) at a median age of 5 years, and only 25% of survivors were free of significant neurodevelopmental deficit at follow-up.^[30] A study of 41 CDH survivors (both ECMO- and non-ECMO-treated) found 46% of those treated with ECMO had deficits in developmental outcome at a median age of 24 months.^[27] Five subjects at five years of age had VIQ, PIQ, and FIQ scale scores less than the expected values, and 40% had moderate to severe delays in all three categories. The ECMO-treated survivors were noted to be at increased risk for psychomotor dysfunction and motor delays as well.^[27]

There are relatively few studies describing the neurodevelopmental outcome of CDH survivors *not* treated with ECMO. Bouman *et al* described the outcomes of non-ECMO treated CDH survivors between 8-12 years of age and found only 45% to have IQ scores in the normal range, and 54% to be functioning at expected grade level in school. Additionally, the survivors displayed a higher prevalence of emotional and behavioral problems, and nearly half demonstrated moderate to severe problems in functioning at home, at school, or in relation to peers.^[20] A study of 31 CDH survivors between ages 6 months and 9 years found 23% to have significant neurodevelopmental problems at follow-up, described as

global developmental delay, speech impairment, hearing impairment, and/or visual impairment.^[12] Jakobson *et al* studied 13 non-ECMO treated CDH adolescents at a mean age of 12.9 years and found the subjects to have poorer oral-motor and visual-motor integration skills compared to typically developing peers.^[31] Finally, Frisk *et al* compared the cognitive outcomes of 15 non-ECMO treated CDH survivors with 18 matched term controls between ages 10-16 years. The authors found 15.4% of the CDH survivors versus 0% of controls had clinically significant impairment on the full-scale IQ measure. Similar trends were found for the verbal and performance subtests. Further, parents of CDH survivors reported higher rates of executive dysfunction in their children compared with parents of controls.^[32] In our study of both ECMO and non-ECMO treated CDH survivors, ECMO treatment was significantly associated with persistent NCD at school age. None of the infants who survived without neurocognitive delay were treated with ECMO in the neonatal period. This supports our practice of using ECMO for rescue rather than as a prophylactic strategy, and provides impetus to study interventions aimed at improving neurocognitive outcomes among ECMO-treated infants.

In a report from the CDH Study Group, diaphragmatic defect size was determined to be the most significant factor affecting survival; the authors surmised that defect size may be a surrogate marker for degree of pulmonary hypoplasia.^[33] Valfrè *et al* studied 61 CDH survivors to investigate the relationship between patch repair and outcome, and found patched survivors had poorer weight gain and higher rates of GER compared to patients with a primary repair.^[34] CDH infants with patch repair of the diaphragmatic defect have been shown to have increased rates of neurocognitive impairment.^[27, 29] It is plausible that a larger diaphragmatic defect necessitating a patch repair indicates a more severe underlying disease process with a greater degree of pulmonary hypoplasia, and may be predictive of worse outcome.

The association between post-operative use of iNO and adverse developmental outcome may reflect the impact of impaired cerebral blood flow and oxygenation in the setting of PPHN. A recent study of neurodevelopmental outcomes in 27 PPHN survivors at a mean age of 3.4 years showed 26% to have behavioral problems and 22% with language disturbances.^[35] The authors related the high incidence of neurologic deficits to illness severity rather than specific treatment modalities. Rosenberg *et al* investigated school age outcomes of infants treated with iNO for PPHN and did not find an association between iNO and adverse neurodevelopmental outcome.^[36] Interestingly, though, a trend towards poorer outcome in children with CDH treated with iNO was noted, with a 33% rate of moderate or severe handicap in this subgroup.

We did not find an association between abnormalities on neuroimaging studies and poor neurocognitive outcome, which may in part be explained by the small size of our cohort. In a larger study, Tracy *et al* examined 41 CDH survivors and found 46% to have motor problems at age 1; this increased to 70% at age 3. In their study, abnormalities on postnatal imaging were predictive of motor problems at 1 year of age.^[37] Although we did not specifically measure motor outcome in this early school-age study, 2 survivors had neurologic findings consistent with a diagnosis of cerebral palsy. We also did not find an association between BMI at follow-up and neurodevelopmental outcome. Cortes *et al* noted severe growth failure among 16 CDH survivors at both 1 and 2 years of age but did not demonstrate a significant association between failure to thrive and poor neurodevelopmental outcome.^[38] We noted a trend towards birth weight being protective against NCD: larger babies were less likely to have NCD at school age (although this finding was not statistically significant). A similar correlation between higher birth weight and improved survival has been demonstrated in previous studies.^[30, 39, 40]

Developmental and behavioral problems seen at an early age may be predictive of continued difficulties throughout childhood. In a UK study of ECMO survivors, children classified with moderate to severe disability at age 4 continued to have disability at age 7, and the authors noted a clearer profile of learning difficulties and behavior problems in the older group.^[41] Similarly, in our study, all infants who were delayed at 18-22 months continued to show neurocognitive impairment at school age. Furthermore, the infants who scored within the average range on early neurodevelopmental testing maintained average scores at early school age, demonstrating excellent concordance between measures of neurodevelopment in the preschool age with those used to assess cognitive and language ability at school age.

Walker *et al* emphasize the importance of providing accurate prognostic information to families as they strive to make informed decisions regarding available treatment options on behalf of their infants.^[42] Additionally, outcome prediction aids in allocation of resources to those at highest risk of ongoing disability. Among other factors, Danzer *et al* found patch repair and need for ECMO to be associated with borderline or delayed neurodevelopmental outcome.^[27] In our cohort, all children who were treated with ECMO or who received post-operative iNO had NCD at school age. Also, in our study, survivors who demonstrated impairment at preschool age were likely to experience continued difficulties with behavior and learning throughout childhood. CDH survivors meeting these criteria might benefit from close monitoring and aggressive intervention in a multidisciplinary follow-up program to maximize their individual neurodevelopmental potential.

This study is one of the first to examine school age outcomes in a cohort of CDH survivors. Our study is limited by several factors, the most important being the small number of enrolled subjects. Due to the relative rarity of this condition, combined with the inherent difficulties involved in long-term follow-up studies, single-center reports of CDH outcomes often involve small numbers of subjects. Ideally we would have preferred to enroll all eligible subjects; however, we did not find any major differences in demographic or treatment variables between those children who were enrolled and those who were eligible but not enrolled. The limited availability of appropriate standardized neuropsychological measures for predominately Spanish-speaking children prevented inclusion of these children in this and in similar studies. Though it is unlikely that any children with significant hearing loss were missed, CDH survivors are known to be at risk for sensorineural hearing loss. This issue may need to be more systematically examined in subsequent school age CDH outcome studies.

Conclusion

Over the past two decades, significant advancements in the fields of neonatology and pediatric surgery have led to improved overall survival of infants with CDH in high-volume centers. This improvement in survival has likely led to increased long-term morbidity in infants who previously would have died. Poor neurodevelopmental outcome in infants with CDH is likely the result of a combination of multiple factors; therefore, CDH survivors should be considered at significant risk for neurocognitive delay and followed regularly in a multidisciplinary clinic to readily identify and effectively treat ongoing medical and developmental challenges.

Certain perinatal and pre-discharge factors may be useful in identifying infants at increased risk for persistent learning difficulties throughout childhood, namely, a large diaphragmatic defect necessitating a patch repair, treatment with ECMO, post-operative use of iNO, and prolonged duration of mechanical ventilation. Further studies investigating the medical and neurodevelopmental outcomes of CDH survivors at school age and beyond are needed to confirm our findings and improve care for these complex and vulnerable patients.

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Abbreviations

BMI	body mass index
CDH	congenital diaphragmatic hernia
ECMO	extracorporeal membrane oxygenation
FIQ	Full Scale IQ
GER	gastroesophageal reflux
iNO	inhaled nitric oxide
NCD	neurocognitive delay
NICU	neonatal intensive care unit
PIQ	Performance Scale IQ
PPHN	persistent pulmonary hypertension of the newborn
RAD	reactive airway disease
TELD	Test of Early Language Development
VIQ	Verbal Scale IQ
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

References

1. Davis CF, Sabharwal AJ. Management of congenital diaphragmatic hernia. Arch Dis Child Fetal Neonatal Ed. 1998; 79:F1–3. [PubMed: 9797617]
2. Langham MR Jr, Kays DW, Beierle EA, et al. Twenty years of progress in congenital diaphragmatic hernia at the University of Florida. Am Surg. 2003; 69:45–52. [PubMed: 12575780]
3. Langham MR Jr, Kays DW, Ledbetter DJ, et al. Congenital diaphragmatic hernia. Epidemiology and outcome. Clin Perinatol. 1996; 23:671–688. [PubMed: 8982563]
4. Nobuhara KK, Lund DP, Mitchell J, et al. Long-term outlook for survivors of congenital diaphragmatic hernia. Clin Perinatol. 1996; 23:873–887. [PubMed: 8982576]
5. Kays DW, Langham MR Jr, Ledbetter DJ, et al. Detrimental effects of standard medical therapy in congenital diaphragmatic hernia. Ann Surg. 1999; 230:340–348. discussion 348–351. [PubMed: 10493481]
6. Azarow K, Messineo A, Pearl R, et al. Congenital diaphragmatic hernia—a tale of two cities: the Toronto experience. J Pediatr Surg. 1997; 32:395–400. [PubMed: 9094001]
7. Boloker J, Bateman DA, Wung JT, et al. Congenital diaphragmatic hernia in 120 infants treated consecutively with permissive hypercapnea/spontaneous respiration/elective repair. J Pediatr Surg. 2002; 37:357–366. [PubMed: 11877648]
8. Colvin J, Bower C, Dickinson JE, et al. Outcomes of congenital diaphragmatic hernia: a population-based study in Western Australia. Pediatrics. 2005; 116:e356–363. [PubMed: 16140678]
9. Stege G, Fenton A, Jaffray B. Nihilism in the 1990s: The True Mortality of Congenital Diaphragmatic Hernia. Pediatrics. 2003; 112:532–535. [PubMed: 12949279]
10. Cohen-Katan S, Newman-Heiman N, Staretz-Chacham O, et al. Congenital diaphragmatic hernia: short-term outcome. Isr Med Assoc J. 2009; 11:219–224. [PubMed: 19603595]

11. Bagolan P, Morini F. Long-term follow up of infants with congenital diaphragmatic hernia. *Semin Pediatr Surg.* 2007; 16:134–144. [PubMed: 17462566]
12. Crankson SJ, Al Jadaan SA, Namshan MA, et al. The immediate and long-term outcomes of newborns with congenital diaphragmatic hernia. *Pediatr Surg Int.* 2006; 22:335–340. [PubMed: 16456659]
13. Kamata S, Usui N, Kamiyama M, et al. Long-term follow-up of patients with high-risk congenital diaphragmatic hernia. *J Pediatr Surg.* 2005; 40:1833–1838. [PubMed: 16338300]
14. Jaillard SM, Pierrat V, Dubois A, et al. Outcome at 2 years of infants with congenital diaphragmatic hernia: a population-based study. *Ann Thorac Surg.* 2003; 75:250–256. [PubMed: 12537224]
15. Muratore CS, Utter S, Jaksic T, et al. Nutritional morbidity in survivors of congenital diaphragmatic hernia. *J Pediatr Surg.* 2001; 36:1171–1176. [PubMed: 11479850]
16. Su W, Berry M, Puligandla PS, et al. Predictors of gastroesophageal reflux in neonates with congenital diaphragmatic hernia. *J Pediatr Surg.* 2007; 42:1639–1643. [PubMed: 17923189]
17. Fasching G, Huber A, Uray E, et al. Gastroesophageal reflux and diaphragmatic motility after repair of congenital diaphragmatic hernia. *Eur J Pediatr Surg.* 2000; 10:360–364. [PubMed: 11215775]
18. Muratore CS, Kharasch V, Lund DP, et al. Pulmonary morbidity in 100 survivors of congenital diaphragmatic hernia monitored in a multidisciplinary clinic. *J Pediatr Surg.* 2001; 36:133–140. [PubMed: 11150452]
19. Trachsel D, Selvadurai H, Bohn D, et al. Long-term pulmonary morbidity in survivors of congenital diaphragmatic hernia. *Pediatr Pulmonol.* 2005; 39:433–439. [PubMed: 15704183]
20. Bouman NH, Koot HM, Tibboel D, et al. Children with congenital diaphragmatic hernia are at risk for lower levels of cognitive functioning and increased emotional and behavioral problems. *Eur J Pediatr Surg.* 2000; 10:3–7. [PubMed: 10770239]
21. Morini F, Capolupo I, Masi R, et al. Hearing impairment in congenital diaphragmatic hernia: the inaudible and noiseless foot of time. *J Pediatr Surg.* 2008; 43:380–384. [PubMed: 18280294]
22. Peetsold MG, Huisman J, Hofman VE, et al. Psychological outcome and quality of life in children born with congenital diaphragmatic hernia. *Arch Dis Child.* 2009; 94:834–840. [PubMed: 19531530]
23. Cortes RA, Keller RL, Townsend T, et al. Survival of severe congenital diaphragmatic hernia has morbid consequences. *J Pediatr Surg.* 2005; 40:36–46. [PubMed: 15868556]
24. Chen C, Jeruss S, Chapman JS, et al. Long-term functional impact of congenital diaphragmatic hernia repair on children. *J Pediatr Surg.* 2007; 42:657–665. [PubMed: 17448762]
25. Tracy ET, Mears SE, Smith PB, et al. Protocolized approach to the management of congenital diaphragmatic hernia: benefits of reducing variability in care. *J Pediatr Surg.* 2010; 45:1343–1348. [PubMed: 20620342]
26. Bayley N. Bayley Scales of Infant Development. second edition. The Psychological Corporation; 1993.
27. Danzer E, Gerdes M, Bernbaum J, et al. Neurodevelopmental outcome of infants with congenital diaphragmatic hernia prospectively enrolled in an interdisciplinary follow-up program. *J Pediatr Surg.* 2010; 45:1759–1766. [PubMed: 20850617]
28. McGahren ED, Mallik K, Rodgers BM. Neurological outcome is diminished in survivors of congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation. *J Pediatr Surg.* 1997; 32:1216–1220. [PubMed: 9269973]
29. D'Agostino JA, Bernbaum JC, Gerdes M, et al. Outcome for infants with congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation: The first year. *J Pediatr Surg.* 1995; 30:10–15. [PubMed: 7722808]
30. Davis PJ, Firmin RK, Manktelow B, et al. Long-term outcome following extracorporeal membrane oxygenation for congenital diaphragmatic hernia: the UK experience. *The Journal of Pediatrics.* 2004; 144:309–315. [PubMed: 15001933]
31. Jakobson LS, Frisk V, Trachsel D, et al. Visual and fine-motor outcomes in adolescent survivors of high-risk congenital diaphragmatic hernia who did not receive extracorporeal membrane oxygenation. *J Perinatol.* 2009; 29:630–636. [PubMed: 19461591]

32. Frisk V, Jakobson LS, Unger S, et al. Long-term neurodevelopmental outcomes of congenital diaphragmatic hernia survivors not treated with extracorporeal membrane oxygenation. *J Pediatr Surg.* 2011; 46:1309–1318. [PubMed: 21763827]
33. The Congenital Diaphragmatic Hernia Study Group. Defect Size Determines Survival in Infants With Congenital Diaphragmatic Hernia. *Pediatrics.* 2007; 120:e651–657. [PubMed: 17766505]
34. Valfrè L, Braguglia A, Conforti A, et al. Long term follow-up in high-risk congenital diaphragmatic hernia survivors: patching the diaphragm affects the outcome. *J Pediatr Surg.* 2011; 46:52–56. [PubMed: 21238639]
35. Berti A, Janes A, Furlan R, et al. High prevalence of minor neurologic deficits in a long-term neurodevelopmental follow-up of children with severe persistent pulmonary hypertension of the newborn: a cohort study. *Italian Journal of Pediatrics.* 2010; 36:45. [PubMed: 20540801]
36. Rosenberg AA, Lee NR, Vaver KN, et al. School-age outcomes of newborns treated for persistent pulmonary hypertension. *J Perinatol.* 2009; 30:127–134. [PubMed: 19798045]
37. Tracy S, Estroff J, Valim C, et al. Abnormal neuroimaging and neurodevelopmental findings in a cohort of antenatally diagnosed congenital diaphragmatic hernia survivors. *J Pediatr Surg.* 45:958–965. [PubMed: 20438935]
38. Cortes RA, Keller RL, Townsend T, et al. Survival of severe congenital diaphragmatic hernia has morbid consequences. *J Pediatr Surg.* 2005; 40:36–45. discussion 45-36. [PubMed: 15868556]
39. Haricharan RN, Barnhart DC, Cheng H, et al. Identifying neonates at a very high risk for mortality among children with congenital diaphragmatic hernia managed with extracorporeal membrane oxygenation. *J Pediatr Surg.* 2009; 44:87–93. [PubMed: 19159723]
40. Seetharamaiah R, Younger JG, Bartlett RH, et al. Factors associated with survival in infants with congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation: a report from the Congenital Diaphragmatic Hernia Study Group. *J Pediatr Surg.* 2009; 44:1315–1321. [PubMed: 19573654]
41. McNally H. United Kingdom Collaborative Randomized Trial of Neonatal Extracorporeal Membrane Oxygenation: Follow-up to Age 7 Years. *Pediatrics.* 2006; 117:e845–e854. [PubMed: 16636114]
42. Walker K, Holland AJ, Winlaw D, et al. Neurodevelopmental outcomes and surgery in neonates. *J Paediatr Child Health.* 2006; 42:749–751. [PubMed: 17096707]

Figure 1.
Flow diagram of study participants.

Table 1

Characteristics of entire CDH cohort and enrolled versus not enrolled survivors

Variable	CDH Cohort (n = 43)	CDH Survivors (n = 27)	
		Enrolled (n= 16)	Not enrolled (n = 11)
Demographic data			
Birth weight (g) – median (range)	3000 (1705, 4445)	3293 (2560, 4445)	2900 (1705, 3595)
Gestational age (weeks) – median (range)	39 (32, 41)	39 (34, 41)	38 (32, 41)
Female sex – n (%)	19 (44)	5 (31)	4 (36)
Black race – n (%)	10 (23)	3 (19)	3 (27)
Inborn – n (%)	25 (58)	9 (56)	6 (55)
Physiologic data			
Apgar score at 5 min – median (range)	7 (1, 9)	7 (4, 9)	8 (5, 9)
Congenital cardiac defect – n (%)	7 (16)	2 (13)	3 (27)
Left-sided diaphragmatic defect – n (%)	27 (63)	9 (56)	8 (73)
Abnormal brain imaging (CT or MRI) ¹ – n (%)	10 (63)	3 (50)	2 (40)
Treatment data			
Patch repair – n (%)	16 (46)	7 (44)	2 (18)
ECMO ² – n (%)	14 (33)	4 (25)	1 (9)
Days of mechanical ventilation – median (range)	12 (1, 154)	11 (2, 154)	7 (2, 41)
Days on ECMO ² – (range)	(0, 22)	(0, 22)	(0, 12)
Pre-operative iNO ³ – n (%)	22 (52)	7 (44)	3 (27)
Post-operative iNO ^{1, 3} – n (%)	14 (39)	4 (25)	3 (27)

¹ Results not applicable for subjects who died prior to surgery or did not have brain imaging performed² Extracorporeal membrane oxygenation³ Inhaled nitric oxide

Table 2Comparison between subjects with and without NCD¹

Variable	Survived with NCD ¹ (n = 7)	Survived without NCD ¹ (n = 9)	P
Demographic data			
Birth weight (g) – median (range)	3000 (2560, 3500)	3475 (2845, 4445)	0.09
Gestational age (weeks) – median (range)	39 (34, 40)	39 (35, 41)	0.61
Female sex – n (%)	2 (29)	3 (33)	0.99
Black race – n (%)	2 (29)	1 (11)	0.76
Inborn – n (%)	5 (71)	4 (44)	0.36
Apgar (5 min) – median (range)	6 (4, 9)	8 (5, 9)	0.11
Congenital cardiac defect – n (%)	1 (14)	1 (11)	0.99
Left-sided diaphragmatic defect – n (%)	4 (57)	5 (56)	0.99
Abnormal brain imaging (CT or MRI) ² – n (%)	1 (25)	0	0.40
Treatment data			
Patch repair – n (%)	6 (86)	1 (11)	0.009
ECMO ³ – n (%)	4 (57)	0	0.019
Days of mechanical ventilation – median (range)	27 (2, 154)	5 (4, 18)	0.049
Days on ECMO ³ – median (range)	10 (0, 22)	0	0.01
Pre-operative iNO ⁴ – n (%)	5 (71)	2 (22)	0.13
Post-operative iNO ⁴ – n (%)	4 (57)	0	0.019

¹Neurocognitive delay, defined as score <80 on Verbal Scale IQ, Performance Scale IQ, Receptive Language, or Expressive Language²Results not applicable for subjects who did not have brain imaging performed³Extracorporeal membrane oxygenation⁴Inhaled nitric oxide

Table 3

Neurocognitive testing scores and percentage scoring within the abnormal range for each.

	Median (range)	< 80 (%)
WPPSI-III Verbal IQ	94 (67, 127)	19
WPPSI-III Performance IQ	88 (59, 116)	25
WPPSI-III Full Scale IQ	89 (58, 121)	19
TELD-III, receptive ^I	98 (65, 115)	13
TELD-III, expressive ^I	88 (70, 118)	33
TELD-III, Spoken Language Quotient ^I	98 (65, 116)	27

^IOne subject unable to complete language measure