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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.

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.

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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.

Congenital diaphragmatic hernia (CDH) occurs in approximately 1 in 3000–5000 live births [1-3], with overall mortality ranging between 40% and 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.

1. Methods

1.1. Subjects

We identified all infants with CDH diagnosed prenatally or within the first 24 h 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, inhaled nitric oxide (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 was approximately equal among the surgeons. Both pediatric surgeons had considerable experience with repair of CDH. All CDH survivors $\geq$ 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.

1.2. 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 aged 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 month through 7 years, 11 months. The TELD-3