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Preschool neurological assessment in congenital diaphragmatic hernia survivors: Outcome and perinatal factors associated with neurodevelopmental impairment

Enrico Danzer [a,b], Marsha Gerdes [a,b], Jo Ann D'Agostino [a,b], Emily A. Partridge [a,b], Casey H. Hoffman-Craven [a,b], Judy Bernbaum [a,b], Natalie E. Rintoul [a,b], Alan W. Flake [a,b], N. Scott Adzick [a,b], Holly L. Hedrick [a,b,*]

[a] The Center for Fetal Diagnosis and Treatment, The Children's Hospital of Philadelphia, Philadelphia, PA, USA
[b] The University of Pennsylvania School of Medicine, Philadelphia, PA, USA

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ABSTRACT

Objective: To evaluate the preschool neurodevelopmental outcome in CDH survivors between 2 and 5 years of age and to identify perinatal and postnatal factors that may be predictive of persistent neurological deficits.
Methods: The study cohort consists of 60 CDH survivors that were enrolled in our prospective, follow-up program between January 2006 and September 2012. Developmental assessment of study participants between 2 and 3 years of age was performed using the Bayley Scales of Infant Development, 3rd Edition (BSID-III). Cognitive outcomes of CDH children older than 3 years of age were evaluated using The Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition (WPPSI-III). Neurodevelopmental delay was defined by a score of $\leq$85 in any of the evaluated composite scores. Severe impairments were defined as a score of $\leq$69 in at least one domain tested.
Results: Mean follow-up for children assessed by BSID-III (n = 42) and WPPSI-III (n = 18) was 28 ± 4.5 months and 58 ± 4.0 months, respectively. As a group, mean composite and subdomain BSID-III and WPPSI-III scores were within the expected normal range. For the BSID-III group, 9 (22%) had mild deficits in at least one domain, and 6 (14%) had severe deficits in at least one. Only 3 (7%) patients demonstrated severe neurological delays for all BSID-III composite scales. For the WPPSI-III group, 4 (22%) patients scored within the borderline-delayed range for at least one subscale and only one (6%) child had a WPPSI-III VIQ score in the severe delay range. Abnormal muscle tonicity was found in 35% (hypotonicity 33%, hypertonicity 2%). Need for ECMO, prolonged ventilation, hypotonicity, and other surrogate markers of disease severity ($P<0.05$) were associated with borderline or delayed neurological outcome.
Conclusion: The majority of CDH children are functioning in the average range at early preschool and preschool age. Neuromuscular hypotonicity is common in CDH survivors. CDH severity appears to be predictive of adverse neurodevelopmental outcome.

1. Introduction

Congenital diaphragmatic hernia (CDH) is one of the most common birth defects with an estimated incidence of 1 in 2500 births. The clinical spectrum of CDH depends on the severity of both fixed (pulmonary and vascular hypoplasia) and reversible (pulmonary vascular reactivity) components and affected neonates usually present with respiratory distress shortly after birth that may be mild or so severe to be incompatible with life [1].

Over the past several decades, advances in surgical techniques, neonatal intensive care, ECMO, and medical therapies have significantly lowered mortality rates for children with CDH. Survivors are, however, at risk for neurodevelopmental and neurofunctional morbidity [2]. With increased survival rates, the focus of clinical research in the CDH population has transitioned from short-term surgical survival to the assessment of long-term morbidity. Neurodevelopmental dysfunction has been recognized as the most common and potentially most disabling outcome of CDH and its treatment [2–8]. Multiple studies have evaluated potential mechanisms of short-term neurodevelopmental dysfunction during infancy [3,5,6,9,10]. In an initial report of 41 CDH survivors prospectively enrolled in our multidisciplinary follow-up program, called the Pulmonary Hypoplasia Program, we found various degrees of developmental and/or functional delays in more than 50% of the infants during the first 2 years of life [6]. Most CDH survivors, however, may have multi-organ involvement and may

* Corresponding author at: The Center for Fetal Diagnosis and Treatment, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104, USA. Tel.: +1 215 590 2733; fax: +1 215 386 4036.
E-mail address: hedrick@email.chop.edu (H.L. Hedrick).

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require prolonged recovery periods. As a result it is not surprising that early neurodevelopment may be delayed. On the other hand, while some disabilities may be transient, others might be very subtle in young infants and the extent of impairment is often not fully recognized until later in life when certain cognitive and higher executive functioning skills are required.

Although it has been recognized that neurological assessments during preschool age are relatively stable and predictive of outcome and function into adolescence and early adulthood, limited information on early preschool and preschool neurodevelopmental outcomes in CDH survivors is available [2,11,12]. An improved understanding of which CDH patients are likely to experience longer-term neurodevelopmental disabilities is critical for parent counseling and the provision of timely intervention for the individual. Given the paucity of preschool data, the purpose of the current study was to: (1) compare the longer-term neurocognitive and functional outcome of CDH survivors at age 2 to 5 years of age to published normative data and (2) identify perinatal and postnatal factors that may be predictive of persistent neurological deficits.

2. Material and methods

2.1. Ethics statement

The Institutional Review Board, Committee for Protection of Human Subjects of The Children's Hospital of Philadelphia approved this study and all parents or legal guardians gave written informed consent for their children (IRB 2004-05-3779).

2.2. Patient population

This was a cross-sectional review of prospectively collected data on developmental outcome in CDH survivors enrolled in our follow-up program between January 2006 and September 2012. All CDH survivors born during the study period who enrolled in the follow-up program were eligible. Among this cohort, subjects who underwent neurodevelopmental assessment at 2 years and older were identified; this group forms the study population for this report. The study group included premature infants, low birth weight as well as full term neonates with CDH and additional concomitant congenital malformation (e.g. lung lesions, giant omphalocele or non-cyanotic cardiac malformations).

2.3. Perinatal and postnatal standardized management

Our protocol for the perinatal and postnatal management of children with prenatally diagnosed CDH has been previously described [1,6,13]. Briefly, the initial evaluation of all CDH patients referred to the Center for Fetal Diagnosis and Treatment at the Children's Hospital of Philadelphia includes detailed fetal ultrasonography and fetal ultrafast MRI. Assessment includes confirmation of diagnosis, the type of CDH, liver position, lung-to-head ratio (LHR), and the presence of other fetal anomalies. Fetal echocardiography and Doppler flow measurements were performed to assess cardiac anatomy and function. After evaluation, all patients underwent nondirective counseling for pregnancy management options. Fetal liver position is determined by ultrasound evaluation and confirmed by MRI. Liver position is considered to be "up" if any portion of the liver is in the chest above the normal level of the diaphragm and to be "down" if the liver is completely within the abdomen [13,14].

The postnatal ventilatory management in the neonatal intensive care unit utilizes a lung-preservation strategy [6,13,15]. The mode of ventilation is aimed at administering only enough pressure to maintain preductal oxygen saturations greater than 85%. High frequency ventilation is reserved for neonates that continue to have hypercapnia refractory to conventional ventilation. If these therapies failed, neonates were then placed on venoarterial extracorporeal membrane oxygenation (ECMO). The indications for ECMO included failure of conventional therapy as defined by inability to maintain preductal oxyhemoglobin saturations greater than 85%, peak inspiratory pressure greater than 28 cm H_2O, mean airway pressure greater than 15, pressor-resistant hypotension, or inadequate oxygen delivery with development of metabolic acidosis. Relative contraindications to ECMO included GA less than 34 weeks and weight less than 2.0 kg. Repair of the CDH was performed in a delayed fashion once medical stability was achieved, the pulmonary vasculature became less reactive (absence of shunting), or weaning from ECMO was anticipated (sometimes prior to decannulation). The operating surgeon determined the need for patch placement based on the size of the diaphragmatic defect.

2.4. Data collection

Perinatal, perioperative and postnatal factors that might independently affect neurodevelopmental and neuromotor outcome such as LHR, liver position, gestational age at delivery, birth weight, APGAR scores, ventilator days, ECMO need, perioperative use of sildenafil, inhaled nitric oxide, and inotropes, type and age at repair, complications, O_2 requirement at day of life 30, length of stay, and others were obtained from maternal prenatal charts and neonatal hospital records.

2.5. Assessment procedures

Growth parameters including weight, length, and head circumference were measured and compared to standard reference curves. Corrected age was used to plot measurements for preterm infants. The child's race and ethnicity were assessed by parental report.

Developmental assessment of study participants between 2 and 3 years of age was performed using the Bayley Scales of Infant Development, 3rd Edition (BSID-III) [16]. The third edition of the BSID was published in 2006 and has been validated in at-risk populations between ages of 1 to 42 months. BSID-III provides composite scores for cognitive, language, and motor outcome [16]. The normalized population mean and SD of each composite score is 100 ± 15. The cognitive scale contains items that assess memory, problem solving, and counting skills. The language scale evaluates both receptive and expressive language; evaluating the child's understanding and use of words and gestures. The motor scale assesses fine (e.g. dexterity) and gross (e.g. walking) motor skills.

Cognitive outcomes of CDH children older than 3 years of age were evaluated using The Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition (WPPSI-III) [17]. The WPPSI-III is a widely used, standardized assessment tool comprised of 10 verbal and performance subtests (e.g. reasoning, comprehension, conceptualization, visual-spatial analysis, etc.) and yields a verbal intelligence quotient (VIQ), performance intelligence quotient (PIQ), full intelligence quotient (FIQ), and processing speed (PS) scores. Each of the composite scores has an expected mean of 100 and a standard deviation (SD) of 15.

Visual-motor integration for children older than 3 years was assessed using the Beery–Buktenica Developmental Test of Visual Motor Integration (VMI; mean: 100 ± 15), a simple copying task that assesses the child's fine-motor and visual motor coordination skills [18].

Overall scores were grouped as average, borderline, and delayed based on SD intervals (85–115, 70–84, and ≤ 69, respectively). If a child was judged to be too developmentally impaired to complete the tasks, a score was imputed by assigning him or her the lowest possible score for the specific test.

The neuromuscular examination (active tone, passive tone, reflexes, gross motor abilities, and fine motor abilities) was classified