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Younger gestational age is associated with increased risk of adverse neurodevelopmental outcome during infancy in congenital diaphragmatic hernia

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ABSTRACT

Background: The purpose of the study was to investigate the impact of gestational age (GA) on short-term neurodevelopmental (ND) outcomes in congenital diaphragmatic hernia survivors.
Materials: Between 6/2004 and 2/2013, 135 consecutive CDH patients underwent ND assessment using the Bayley Scales of Infant Development-III at a median follow-up age of 13 months (range, 5–36). ND delay was defined by a score of ≤85 in any of the composite scales. Severe impairment was defined as a score of ≤69 in at least one domain. The effect of GA was evaluated as continuous and categorical variables. GA at delivery was grouped into full term (39–41 weeks), near term (37–38), late preterm (34–36), and preterm (24–33).
Results: Median GA at delivery was 38 weeks (range, 24–41). Fifty (37%) patients were delivered full term, 59 (44%) near term, 16 (12%) late preterm, and 10 (7%) preterm. CDH children born before 39 weeks' gestation were more likely to score below average ($P = 0.005$) with corrected age for at least one composite score compared to full term peers. Cognitive ($P = 0.06$) and language ($P = 0.08$) scores tended to be lower in the near-term and late-preterm group compared to full-term CDH infants. Patients born near term and late preterm had significantly lower motor composite and fine motor scores compared to full-term children ($P = 0.009$ and $P < 0.01$, respectively). Preterm children scored the lowest in all composite scales ($P < 0.05$).
Conclusions: Compared to term infants, not only preterm but also late preterm and near-term CDH children carry an increased risk of ND delays. Motor performance appears most susceptible to earlier delivery.

Congenital diaphragmatic hernia (CDH) is a common congenital defect with an estimated prevalence of one per approximately 3000 live births. Over the past two decades, innovations in neonatal care and surgical techniques have resulted in improved survival. With improved survival, however, it has been increasingly recognized that neurodevelopmental disabilities and impaired functional outcome are common in children with CDH [1,2]. Although the etiology of neurological problems is most likely multifactorial, several patient-related potentially nonmodifiable factors such as disease severity, associated anomalies, lower socioeconomic status and others are known risk factors associated with adverse neurodevelopmental outcome [3–7]. Hence, identification of modifiable factors as targets for therapeutic interventions might be necessary to improve neurodevelopmental disabilities.

The risks of premature birth have been well described [8]. There is also increasing evidence that late-preterm and/or near-term delivery is associated with an increased incidence of respiratory distress syndrome, hypothermia, feeding difficulties, and apnea [9]. Additionally, recent data suggest that births before 39 weeks' gestation may also affect neurodevelopmental outcome [10–13].

The optimal gestational age of delivery for fetuses with CDH remains unknown. Early delivery might be indicated for maternal or fetal health issues. However, increased prenatal diagnosis of CDH has led to an increase in elective delivery, often before 39 weeks' gestation. Recently, late-preterm and near-term delivery of CDH patients has been shown to be associated with increased morbidity and mortality during the neonatal period [14,15]. However, there are no data to determine whether delivery before term affects neurodevelopmental and functional outcomes in CDH survivors.

The primary objective of the current study was to investigate the impact of gestational (GA) on neurodevelopmental outcomes infants with CDH.

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1. Material and methods

1.1. 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 2004-5-3779).

1.2. Patient population

This was a retrospective review on neurodevelopmental and neurofunctional outcome in CDH survivors enrolled in our follow-up program between June 2004 and February 2013. All CDH survivors born during the study period who enrolled in the follow-up program and underwent neurological assessment were eligible.

1.3. Perinatal and postnatal management

As previously described, our CDH patients are treated according to a specific perinatal and postnatal management protocol [3,4,16,17]. Briefly, all CDH patients referred to the Center for Fetal Diagnosis and Treatment at the Children's Hospital of Philadelphia undergo a comprehensive prenatal imaging evaluation including ultrasonography, echocardiography, and MR imaging. After evaluation, all patients undergo nondirective counseling for pregnancy management options. The postnatal ventilator management in the neonatal intensive care unit utilizes a lung-preservation strategy similar to that of infants with other causes of pulmonary hypoplasia (e.g. giant omphalocele, fetal lung lesions). High frequency ventilation is reserved for neonates that continue to have hypercapnia refractory to conventional ventilation. Indication for initiation of venoarterial extracorporeal membrane oxygenation (ECMO) therapy included failure of medical management to avoid ventilator-related lung injury or persistent hypotension/acidosis. The operating surgeon determines the timing of repair based upon comorbidities and clinical stability as well as the need for patch repair based upon the size of the diaphragmatic defect.

1.4. Follow-up and neurodevelopmental assessment

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 during infancy was performed using the Bayley Scales of Infant Development, 3rd Edition (BSID-III) [18] during routine follow-up visits. The third edition of the BSID was published in 2006 and has been validated in at-risk populations between the ages of 1 and 42 months. BSID-III provides composite scores for cognitive, language, and motor outcome. The normalized population mean and SD of each composite score are 100 ± 15. 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. To minimize observer bias, only 2 psychologists administered neurodevelopmental testing (CH, MG). Their interrater administration and scoring are established on a yearly basis and are 100% in agreement. The neuromuscular examination (active tone, passive tone, reflexes, gross motor abilities, and fine motor abilities) was classified as normal if no abnormalities affecting motor skills were noted, suspect if a moderate degree of abnormality was noted, and abnormal if functionally significant abnormalities of tone, reflexes, or motor skills were present. Each child's last available neurodevelopmental and neurological (e.g. muscle tone and strength) assessment was used for analysis.

1.5. Definition of neurodevelopmental delay

In order to capture the majority of CDH survivors who would be expected to experience at least some degree of impairments, neurodevelopmental delay was defined by a score of ≤85 in any of the evaluated composite scores [3,4,16]. Further severe impairments were defined as a score of ≤69 in at least one domain tested.

1.6. Definition of gestational age at birth periods

According to the guidelines set forth by the American Medical Association Workgroup for Defining Term Pregnancy, gestational age at delivery was grouped into full term (39–41 weeks), near term (37–38), late preterm (34–36), and preterm (24–33) [19]. For inborn patients, type and indications for delivery as well as gestational age at birth were extrapolated from hospital charts. For outborn CDH children this information was collected from available transfer records. Types of delivery were grouped into spontaneous vaginal delivery, planned cesarean section, induced vaginal delivery, and emergent cesarean section. Indication for delivery was divided into nonmedical (e.g. absence of maternal or fetal indications) and medical reasons (e.g. preeclampsia/eclampsia, placental insufficiency, fetal distress, preterm rupture of membrane, preterm labor, IUGR, twin pregnancy, repeat cesarean section, etc.).

1.7. Statistical analysis

Continuous data are presented as means ± SD (median, range). Categorical data are presented as proportions. The differences between groups and developmental outcomes were determined using Student's t, one-way ANOVA, or linear regression, depending on the type of outcome variable. Outcome variables were analyzed by logistic regression or ordinal logistic regression, depending on the type of outcome variable. One-sample t-test was used to compare the mean BSID-III score of outcome to the population mean. P values less than .05 were considered statistically significant. All analyses were conducted in Stata version 12.0 (College Station, TX, USA).

2. Results

2.1. Patient population

Between June 2004 and February 2013, 135 CDH survivors were eligible and enrolled in our prospective multidisciplinary Pulmonary Hypoplasia Program. All returned for neurodevelopmental assessment at least once during the study period. For the entire cohort, median gestational age at delivery was 38 weeks (range, 24–41). Using the American Medical Association Workgroup for Defining Term Pregnancy categories, 50 (37%) patients were delivered full term, 59 (44%) near term, 16 (12%) late preterm, and 10 (7%) preterm.

Baseline, clinical, and surgical characteristics for the entire cohort and the GA subgroups are reported in Table 1. Gestational age and birth weight significantly differed between groups ($P < 0.0001$). CDH infants born at earlier gestational age had a significantly higher incidence of in-hospital morbidities than those born at term as reflected by the need for prolonged ventilatory support, delays in enteral feeding, overall length of NICU stay, and others (for all $P < 0.05$). As summarized in Table 2, the majority of CDH infants born full term or late term were delivered for nonmedical reasons by either spontaneous/induced vaginal delivery or planned cesarean section. As expected late-preterm and preterm patients were more likely be born by induced vaginal delivery or emergent cesarean section owing to maternal and/or fetal complications.