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Neonatal

Growth trajectory and neurodevelopmental outcome in infants with congenital diaphragmatic hernia

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ABSTRACT

Purpose: The purpose of this study was to evaluate the impact of impaired growth on short-term neurodevelopmental (ND) outcomes in CDH survivors.
Methods: Between 9/2005–12/2014, 84 of 215 (39%) CDH survivors underwent ND assessment at 12 months of age using the BSID-III.
Results: Mean cognitive, language, and motor scores were 92.6 ± 13.5, 87.1 ± 11.6, and 87.0 ± 14.4, respectively (normal 100 ± 15). 51% of patients scored 1 SD below the population mean in at least one domain, and 13% scored 2 SD below the population mean.
Group-based trajectory analysis identified two trajectory groups ('high' and 'low') for weight, length, and head circumference (HC) z-scores. (Fig. 1) 74% of the subjects were assigned to the 'high' trajectory group for weight, 77% to the 'high' height group, and 87% to the 'high' HC group, respectively. In multivariate analysis, longer NICU stay ($p < 0.01$) was associated with lower cognitive scores. Motor scores were 11 points higher in the 'high' HC group compared to the 'low' HC group ($p = 0.05$). Motor scores were lower in patients with longer NICU length of stay ($p < 0.001$).
Conclusions: At 1 year, half of CDH survivors had a mild delay in at least one developmental domain. Low HC trajectory was associated with worse neurodevelopmental outcomes.
Type of study: Prognosis Study/Retrospective Study.
Level of evidence: Level II.

Congenital diaphragmatic hernia (CDH) is a complex congenital defect that affects approximately 1 in every 3000 live births [1]. Herniation of abdominal viscera into the thoracic cavity compresses the developing fetal lungs and results in pulmonary hypoplasia and pulmonary hypertension, with a mortality rate estimated between 20 and 60% [2–4]. While the mortality rate has declined in recent years, survivors suffer multiple comorbidities, including neurodevelopmental disabilities.

The etiology of neurodevelopmental disability is complex and multidimensional including medical, surgical, and socioeconomic factors [5,6]. Several risk factors associated with neurodevelopmental disabilities in patients with CDH have been reported: disease severity, associated anomalies, socioeconomic status, gestational age, and the use of extracorporeal membrane oxygenation (ECMO) [7–13].

In other high risk populations, such as infants with congenital heart disease and extreme prematurity, impaired growth has been associated with worse neurodevelopmental outcomes [14,15]. Infants with failure to thrive have higher rates of behavioral and cognitive difficulties when they enter school [16,17], and patients with CDH are also at high risk for poor growth and failure to thrive [18–20].

As part of our Pulmonary Hypoplasia Program at The Children's Hospital of Philadelphia, survivors with CDH underwent neurodevelopmental testing at 12 months of age. In addition, patient growth was measured longitudinally during hospitalization and in follow-up clinic. We used group-based growth trajectory modeling to describe growth patterns in the first year of life. We sought to evaluate the impact of growth trajectory on neurodevelopmental outcomes at 12 months of age. We hypothesized that lower trajectories would be associated with an increased rate of neurodevelopmental disability.

1. Material and methods

We reviewed all patients with CDH who are enrolled in the Pulmonary Hypoplasia Program Database at the Children's Hospital of Philadelphia from September 2005 through December 2014. All CDH

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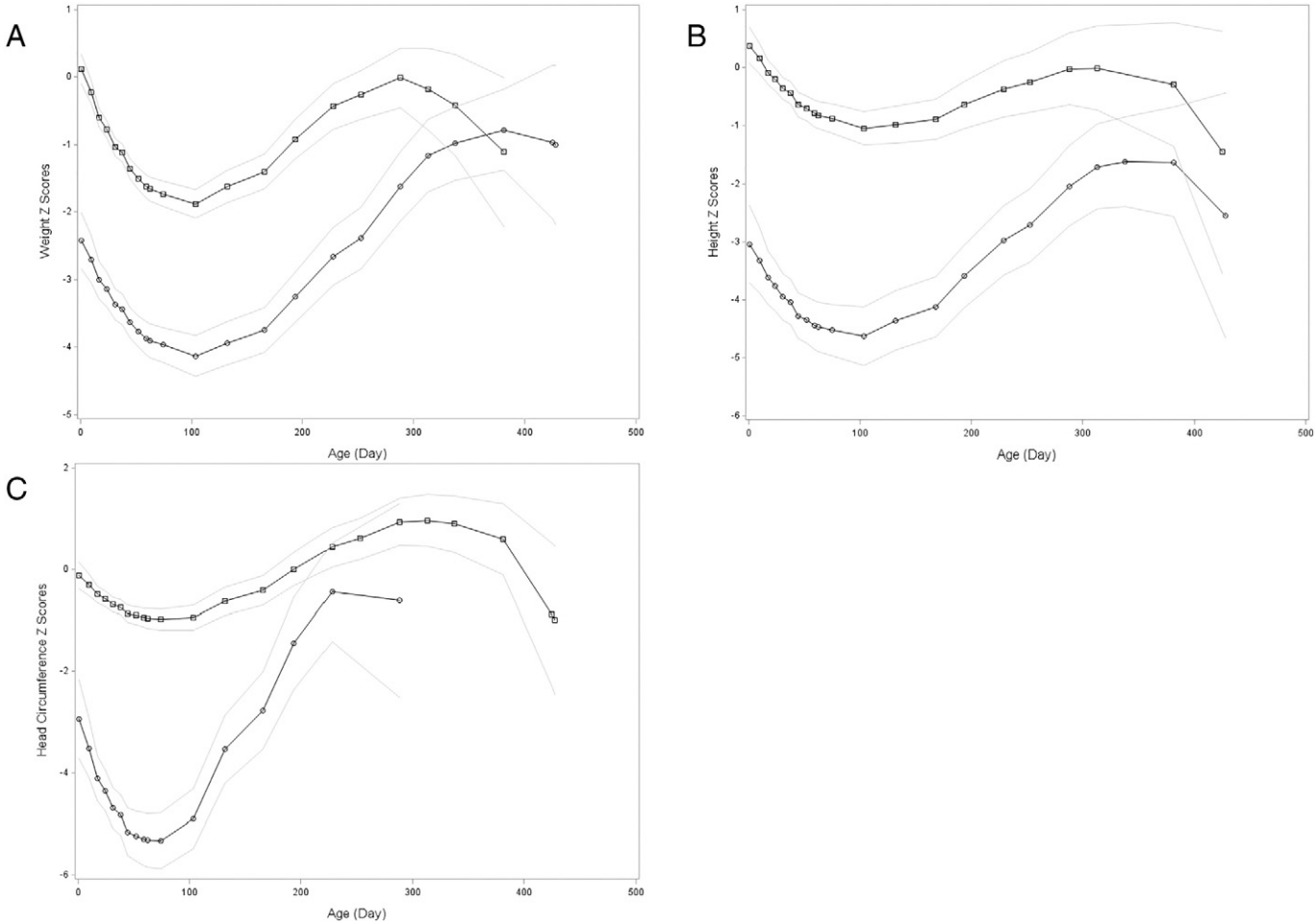

Fig. 1. Trajectories of (A) weight, (B) height, and (C) head circumference *z*-scores over time for 'high' and 'low' growth clusters (N = 84).

survivors born during this time period who also enrolled in NICU follow-up program and underwent neurological assessment, were included in this study. Postnatal care of all study patients was delivered at the Children's Hospital of Philadelphia. This study was approved by the Institutional Review Board at The Children's Hospital of Philadelphia and all parents or legal guardians gave written informed consent for their children to be included our database (IRB 2004–5-3779).

Neurodevelopmental testing was performed using the Bayley Scales of Infant Development, 3rd Edition (BSID-III) [21] at the 12-month follow-up visit by an experienced developmental psychologist. The BSID-III is validated for infants aged 1 to 42 months. The BSID-III provides 3 composite scores: cognitive, language, and motor outcomes. The normalized population mean of each of these composite scores is 100 with a SD of 15. Overall composite scores <85, which is 1 SD below the population mean, was defined as a borderline delay, and an overall composite score <70, 2 SD below the population mean, was defined as delayed. If a child was judged to be too developmentally impaired to complete neurodevelopmental testing, they were assigned the lowest possible score for the specific test.

Patient demographics as well as medical and surgical data were obtained from our Pulmonary Hypoplasia Program Database. Prenatal records were reviewed to determine demographics, CDH side (right vs. left), liver position (above or below the diaphragm), lung-to-head ratio (LHR), and observed (O)/expected (E) LHR. Postnatal records were reviewed for gestational age at birth, timing of CDH repair, need for ECMO, duration of ECMO, NICU length of stay, the need for supplemental oxygen at 30 days of life, and the need for supplemental feeds at NICU discharge.

Postnatal records were reviewed to obtain detailed anthropometric measurements including weight, length, and head circumference. A weight-for-length score was calculated as a marker of malnutrition. Measurements were recorded during NICU hospitalization and at follow-up clinic appointments. All growth data were converted into age-adjusted z-scores based on World Health Organization standards. [22]

1.1. Statistical analyses

We described the data as means with SD, medians with interquartile ranges, or frequencies with percentages, as appropriate. We used a semiparametric group-based trajectory modeling implemented in SAS TRAJ procedure [23] to categorize longitudinal trajectories of weight, length, and head circumference z-scores for each individual. This approach identifies clusters of subjects with similar trajectories using the longitudinally measured growth metrics. Each patient's multiple measures of the growth metrics over time are summarized by a single categorical variable indicating the assignment of trajectory group, which allows for subsequent assessment of association between the growth trajectory and outcomes of interest. The number of trajectory groups was determined by the Bayesian information criteria (BIC) as well as the consideration of the conceptual meaning. This approach accommodates varying frequencies and numbers of anthropomorphic measurements among patients (e.g., a patient with a greater NICU LOS will likely have more data points than a patient with a shorter stay). Patient's medical and surgical variables as well as the derived growth trajectory group indicator were first tested in a univariate analysis for association with the 3 neurodevelopmental composite scores. We then performed a backward stepwise elimination to determine the most parsimonious multivariate model with a p value cutoff of 0.2. Statistical analysis was