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Growth in children with congenital diaphragmatic hernia during the first year of life☆,☆☆,★,★★

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ABSTRACT

Purpose: Infants with congenital diaphragmatic hernia (CDH) have high rates of mortality and long-term morbidity, including poor growth and failure to thrive. The aim of this study was to describe growth patterns during the first year of life in infants with congenital diaphragmatic hernia in a non-ECMO cohort.
Methods: Medical records of infants with CDH admitted to our center between January 2005 and December 2011 were reviewed. Infants with anthropometric measurements at 3, 6 and 12 months were included. Anthropometric measurements were obtained for the first year of life. Logistic regression analyses were performed to find predictive associations with failure to thrive (FTT).
Result: Of the 45 survivors, 38 were seen twice (84%) and 24 (53%) were seen on three occasions to age 12 months. Poor growth was observed with weight being most affected. FTT was present in 63% during the first six months of life. Days of mechanical ventilation were the only predictor of FTT. Besides poor weight gain, height and head circumference were also reduced. However, catch-up growth occurred during the second half of infancy and at age 12 months failure to thrive had reduced by two thirds to 21%.
Conclusions: Poor growth is a common early finding in CDH patients, which improves during infancy. This emphasizes the importance of close follow-up and aggressive nutritional management in CDH patients.
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Infants with congenital diaphragmatic hernia (CDH) have significant rates of mortality and long-term morbidity, which are primarily related to lung hypoplasia and associated pulmonary hypertension [1,2]. In recent years, the survival of CDH infants has progressively improved with survival rates now approaching 90% at some centers [3,4]. Advances in treatment, like extracorporeal membrane oxygenation (ECMO), have been thought to be partly responsible for the improved survival rates in CDH infants [5,6]. However, the beneficial effect of ECMO on survival remains controversial [7,8], and the use of ECMO therapy has been found to be associated with adverse outcomes in CDH survivors [9–11]. With increased survival, the long-term prognosis and quality of life of CDH survivors have become an increasingly important issue.

Failure to thrive (FTT) is a significant comorbidity that has been reported in up to 69% of CDH survivors [12–16]. Catch-up growth in children with CDH has been reported in the second year of life [15], although this finding is not universal [12]. Contributing to poor growth are feeding difficulties and oral aversion, which are reported to occur in up to 27% of CDH infants [12–14]. However, growth over time has been poorly studied in CDH survivors and as such growth patterns during the early years remain unclear.

The aim of this study was to describe the effect of CDH on growth in children during the first year of life.

1. Methods

In this study, medical records of all infants with CDH admitted to the Children's Hospital at Westmead between 1 January 2005 and 31

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December 2011 were reviewed. Infants were treated according to a standardized protocol including gentle ventilation and delayed surgical repair following stabilization. Synchronized conventional ventilation with tidal volume monitoring was the preferred initial ventilator strategy. Inhaled nitric oxide, vasopressor support and high-frequency ventilation were used if infants could not be stabilized with conventional ventilation (Table 1). ECMO was not offered as a routine treatment modality in our center. After hospital discharge, follow-up visits were scheduled in the infant lung clinic on a regular basis. All infants with anthropometric measurements at 3, 6 and 12 months of age were included. Anthropometric measurements were plotted on the World Health Organization 2006 growth charts (http://www.who.int/childgrowth/en/) and *z* scores were calculated. A *z*-score of 0 represents the mean for the reference population. All anthropometric measurements were adjusted for gestation in children born <37 weeks.

FTT was defined as having a *z*-score less than −2 for weight-for-age and/or weight-for-length. After identification of FTT, we searched for variables associated with FTT including prenatal diagnosis, prematurity, birth weight, gender, side of hernia, type of repair, presence of congenital anomalies, presence of moderate to severe pulmonary hypertension (arterial pressures greater than half systemic on echocardiography together with the need for inhaled nitric oxide and/or sildenafil postoperatively), days of mechanical ventilation, supplemental oxygen at discharge, duration of hospital stay and presence of gastroesophageal reflux (GER).

Data were analyzed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL). Categorical variables were compared using χ^2 test or Fisher's Exact test. Student's t tests were used for continuous normally distributed variables and nonparametric tests for nonnormally distributed continuous variables. Logistic regression analyses were performed to find predictive associations with FTT. A *P*-value < 0.05 was considered significant.

2. Results

Fifty-five infants with CDH were admitted to the Children's Hospital at Westmead during the 7-year period of data collection. The overall survival rate during the entire follow-up was 82%. Nine children died in hospital owing to a combination of respiratory failure, pulmonary hypoplasia and persistent pulmonary hypertension. Five children died before undergoing surgical repair and four patients died postoperatively before hospital discharge (age of death: 11, 21, 26, and 112 days). One child died from viral pneumonia after hospital discharge at 10 weeks of age in the emergency department of a regional hospital.

Of the 45 survivors, 38 (84%) were seen twice, between 3 and 12 months of age. A subset of 24 infants (53%) was seen on three occasions (3 months, 6 months and 12 months). Seven patients were lost to follow-up. Infant characteristics are shown in Table 2. Structural heart disease was the most commonly associated congenital anomaly noted in CDH survivors. Minor structural heart disease (atrial septal defect, ventricular septal defect and atrioventricular septal defect) was present in six children and one child had tetralogy of Fallot. Other associated congenital anomalies were malformation of both upper limbs, imperforate anus and a balanced translocation of chromosome 1:16. Moderate to severe pulmonary hypertension was defined by pulmonary arterial pressures greater than half systemic on echocardiography together with the need for inhaled nitric oxide and/or sildenafil postoperatively. Moderate to severe pulmonary hypertension was present in 9/24 (38%) of infants. Pulmonary hypertension, as assessed by echocardiography, had resolved in all by the age of 13 months.

After hospital discharge, 14/24 (58%) of children received supplemental calories with polyjoule, 10/24 (42%) of patients required gastric tube feeding, and 2/24 (8%) of children gastrostomy placement. Poor growth was observed in many infants, especially in early infancy with weight being most affected (Fig. 1). Catch-up growth was observed in a significant proportion of children during infancy. Weight improved from a mean ± standard deviation (SD) *z*-score of −2.07 ± 1.17 at 3 months of age to −0.85 ± 1.32 at 12 months of age.

FTT was present in 15/24 (63%) of the children during the first 6 months of life, however, considerable catch-up growth was observed over the latter part of infancy (Fig. 1). At the age of 12 months, FTT remained in only 5/24 (21%) of the children. When the 38 subjects seen on only two occasions were considered, FTT was present in a similar proportion of the cohort with 50% at 3–6 months and in 19% at 12 months. Days of mechanical ventilation were the only variable predictive of FTT at 6 months of age ($P = 0.03$). We found no predictors for FTT at 12 months of age.

Linear growth was reduced but also improved over time with a mean ± SD *z*-score of −1.36 ± 1.43 at 3 months of age and −0.39 ± 1.30 at 12 months of age. As a consequence of improved weight gain as well as linear growth, weight-for-length scores

Table 1
Respiratory management protocol for CDH infants in the neonatal intensive care unit.

Treatment with synchronized conventional ventilation	PIP max <26 cm H_2O; PEEP: 2–5 cm H_2O*
	Adapt FiO_2 to obtain preductal saturation between 85 and 88% and postductal saturations above 70%
	Ventilator breath rate: 40–60/min to allow permissive hypercapnea (pCO_2 45–65 mm Hg) with a pH of 7.25–7.35†
	Aim for 3–4 ml/kg tidal volume
Indications for inhaled nitric oxide	Presence of pulmonary hypertension confirmed by echocardiography
Indications for vasopressor support	Mean blood pressure <10th percentile for gestational age
Indications for high-frequency ventilation	Preductal saturation <85%
	Respiratory acidosis: pH <7.25 and/or pCO_2 >65 mm Hg

PIP: peak inspiratory pressure; PEEP: positive end expiratory pressure; FiO_2: inspiratory oxygen fraction.

* If oxygenation is a problem consider trialing increased PEEP if chest radiograph reveals under inflation. Also consider a longer inspiratory time and inspiration: expiration ratio of 1:1 to maintain airway pressure.

† Maintain spontaneous respiration if possible.

Table 2
Characteristics of CDH infants.

Characteristics	CDH patients (n = 24)
Gestational age (wk)	37.46 ± 3.08
Birth weight (kg)	2.96 ± 0.73
Gender	
Male	12 (50%)
Female	12 (50%)
Apgar score	
1 min	6 (1–9)
5 min	8 (5–9)
Time of diagnosis	
Prenatal	18 (75%)
Postnatal	6 (25%)
Side of hernia	
Left	20 (83%)
Right	4 (17%)
Type of repair	
Primary repair	14 (58%)
Patch	10 (42%)
Age at surgery (days)	3 (1–14)
Associated congenital anomalies	10 (42%)
Congenital Heart Disease	7 (29%)
Moderate to severe pulmonary hypertension	9 (38%)

Data are presented as mean ± standard deviation, median (range) or number of patients (percentage).

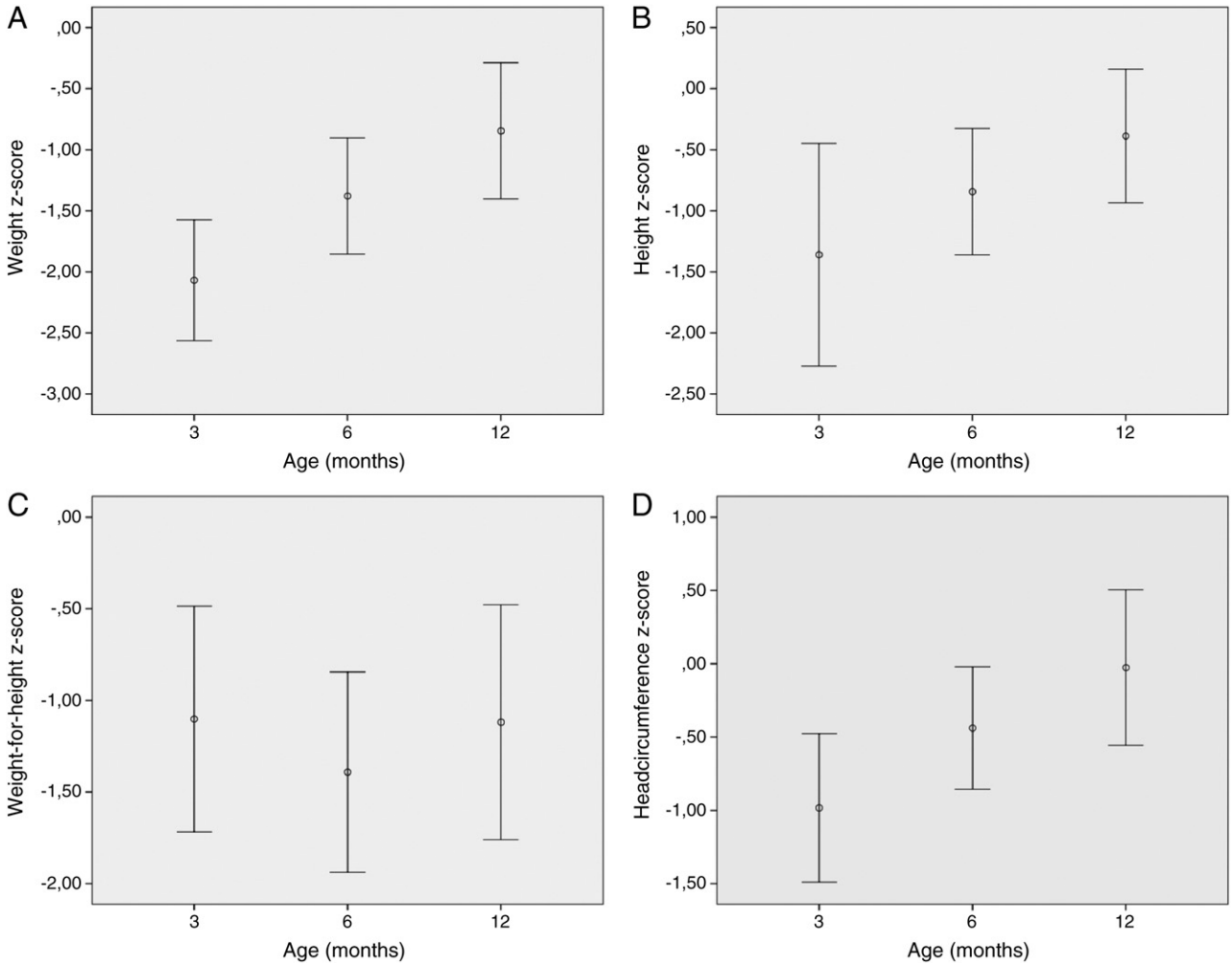


Fig. 1. Weight (A), height (B), weight-for-length (C), and head circumference (D) *z*-scores during the first year of life. The figure presents error bars, indicating mean values and 95% confidence intervals.

remained relatively stable during the first year of life. Weight-for-length mean ± SD *z*-scores were −1.10 ± 0.97, −1.39 ± 1.10, −1.12 ± 1.37, at respectively 3, 6 and 12 months of age. Head circumference was the growth parameter best preserved with mean ± SD *z*-scores of −0.98 ± 1.08, −0.44 ± 0.97, −0.03 ± 1.13 at respectively 3, 6 and 12 months of age.

Twenty-one percent of patients required additional visits to a multidisciplinary feeding clinic owing to persistent feeding difficulties. Oral aversion was observed in 1/24 (4%) of children. Other feeding difficulties reported were: poor suck-swallowing reflex, immature oral skills, feeding difficulties owing to increased work of breathing and GER. The number of children treated for symptomatic GER during infancy was 9/24 (38%). Almost all of these children were successfully managed with antireflux medication, however, only one (4%) child required fundoplication for persistent symptoms despite medical treatment.

3. Discussion

Our survival rate of 82% is consistent with recent studies showing improved survival in CDH patients [3,4,17]. Despite our encouraging survival outcomes, this study indicates that poor growth and FTT are frequent findings in CDH survivors during the first year of life. The cause for poor growth in CDH patients is multifactorial, including increased catabolic stress in the neonatal period, GER, and persistent pulmonary impairment [13]. Poor growth is similarly seen in infants with bronchopulmonary dysplasia during the early months after initial hospitalization, which is caused by their increased work of breathing and higher metabolic rates [18,19]. The number of children with poor growth and FTT in the present cohort is consistent with the findings of others [13]. However, some studies have reported even higher numbers of patients with growth failure [12,15].

Most children in our cohort demonstrated catch-up growth during the first year of life. FTT was present in 63% of children during the first six months of life but remained in only 21% at 12 months of age. Other studies have also reported improved growth with time, but mainly after the first year of life [13,14]. The early follow-up visits in the infant lung clinic and regular medical review together with the elaborate use of calorie-enhanced feeds may have contributed to the faster catch-up growth observed in our patients. Besides poor weight gain, length was reduced in many children during the follow-up period. Linear growth in CDH patients is infrequently described in the literature, and the finding of reduced length in CDH patients has only been reported in one other study [12].

In this study, days of mechanical ventilation were the only predictor of FTT in the first six months of life. This is interpreted to reflect a more severe pulmonary disease phenotype of CDH with poor growth as a consequence of increased respiratory effort or work of breathing, which is consistent with the current literature. One study found an association between FTT and duration of mechanical ventilation as well as hospital stay [20]. Muratore *et al.* have also demonstrated ECMO and the need for oxygen at discharge as

predictors of FTT [13]. GER has also been associated with FTT [13,21]. However, we did not find an association between GER and FTT as was consistent with another study [22]. These differences could be owing to the variable severity of GER present in CDH infants and diagnostic methods. The importance of optimizing early nutrition is likely to improve respiratory status, reduce the metabolic cost of an elevated work of breathing, both in terms of respiratory effort and rate, and allow the utilization of calories for growth.

Oral aversion is another difficult problem that is reported in up to 27% of CDH infants [12–14], however, only one (4%) child in our cohort was diagnosed with oral aversion. Our restrictive approach towards gastrostomy tube placements and early stimulation of oral feeding could be an explanation for the low rate of oral aversion seen.

The incidence of GER found in this study was lower (38%) than reported in most other studies (45%–89%) [12,23]. Further, only one (4%) child required fundoplication in contrast with 19% in another study [13]. This variability in incidence is also likely related to the different diagnostic methods used in studies including pH monitoring, upper gastrointestinal contrast studies or clinical diagnosis of GER, as well as thresholds for initiating treatment.

The strengths of this study are the early follow-up of all four growth parameters in CDH patients during review in the follow-up clinic. Limitations of our study are the retrospective study design and relatively small sample size. Multicenter studies should be encouraged to recruit a sufficient number of CDH patients into a randomized trial of more aggressive feeding initiatives overseen by a dietician to improve growth in early infancy.

4. Conclusion

Poor growth continues to be a common finding in infants with CDH during the first year of life. Close follow-up of growth and nutrition with early aggressive nutritional management is essential. Additional calories should be provided in the first year of life to optimize growth and ameliorate FTT in these infants.

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