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Long-term follow-up of congenital diaphragmatic hernia

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ABSTRACT

Increased survival of patients with congenital diaphragmatic hernia has created a unique cohort of children, adolescent, and adult survivors with complex medical and surgical needs. Disease-specific morbidities offer the opportunity for multiple disciplines to unite together to provide long-term comprehensive follow-up, as well as an opportunity for research regarding late outcomes. These children can exhibit impaired pulmonary function, altered neurodevelopmental outcomes, nutritional insufficiency, musculoskeletal changes, and specialized surgical needs that benefit from regular monitoring and intervention, particularly in patients with increased disease severity. Below we aim to characterize the specific challenges that these survivors face as well as present an algorithm for a multidisciplinary long-term follow-up program.

Introduction

Over the past 20 years, the increased overall survival for infants with congenital diaphragmatic hernia has unveiled new opportunities for long-term follow-up and research on these complicated patients.[1] Although increased patient survival can be, in part, attributable to advances in critical care, including more "gentle" ventilation and physiology-specific strategies, survivors with CDH exhibit chronic lung disease[2–4] as well as neurocognitive delay, gastroesophageal reflux disease (GERD), chest wall deformity, poor growth, and hernia recurrence[5–8] (Table 1). These disease-specific morbidities are frequently identifiable at the time of initial hospital discharge[9] and continue to affect newborn survivors through childhood, adolescence and adulthood, and underscore the need for long-term multidisciplinary follow-up to address their complex medical and surgical needs.[7] The following information is intended to describe the ongoing, long-term morbidity of patients surviving with CDH and also to provide a template for a long-term multidisciplinary CDH follow-up program.

Long-term pulmonary function

Survivors with CDH may require long-term oxygen support, ventilator support with tracheostomy, or pulmonary medical therapy for a variety of reasons including pulmonary hypertension, obstructive airway disease, bronchospasm, or recurrent pneumonias. While most infants with CDH demonstrate clinical improvement over time, many adult survivors have some degree of impairment on pulmonary function testing and require supplemental oxygen or medical therapy, supporting specialized longitudinal multidisciplinary management.[7,10] Pulmonary morbidities include asthma,[2] reduced exercise tolerance,[11] airflow obstruction that may even persist into adulthood,[3] persistent pulmonary hypertension[12] and recurrent lung infections.[7] Bronchopulmonary dysplasia, a chronic respiratory disorder, which occurs in infants after ventilator-induced lung injury and high oxygen concentration requirement, may be prevalent in a higher degree in CDH survivors with pulmonary hypoplasia.[13] Also present can be abnormalities in lung perfusion and ventilation perfusion ratios (V/Q). This pulmonary morbidity as evidenced by V/Q mismatch can persist even beyond the first 5 years of life, particularly if a patch repair was required.[14]

Identifying neonates who may suffer from long-term pulmonary morbidity may begin as early as day of life (DOL) 30. Those who require non-invasive oxygen supplementation or ventilator support at 1 month of life are at significantly increased risk for oxygen use at discharge as well as pulmonary morbidity at 1 and 5 years.[4,15] The use of pulmonary support at DOL 30 may be an even stronger predictor of long-term pulmonary morbidity than defect size, as even patients on room air at DOL 30 had significant rates of inhaler use, ventilation-perfusion (V/Q) mismatch, and asthma years after discharge when compared to controls.[4] Up to 4% of CDH survivors ultimately require tracheostomy for prolonged ventilator support.[16]

Chronic recurrent pneumonia can be an additional morbidity incurred in CDH survivors. Up to 7% of these patients have a pneumonia during their first year of life, and recommendations by the American Academy of Pediatrics include the administration of

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Table 1
Incidence of morbidities in long-term follow-up of patients with CDH.

Morbidity	Estimated frequency
Pulmonary	
Tracheostomy	4%
Decreased exercise tolerance	7–35%
Chronic recurrent pneumonia	7%
Neurodevelopmental	
Neuropathological lesions	50%
Cognitive and motor dysfunction	20–73%
Emotional/behavioral problems	11–23%
Gastrointestinal	
GERD	50–100%
Long-term carcinoma risk	Unclear
Failure to thrive	50–60%
Musculoskeletal	
Pectus deformities	14–80%
Chest asymmetry	48%
Scoliosis	4–50%
Surgical complications	
Recurrence	6–24%
Small bowel obstruction	1–8% (early)
Impact on family	20–40%
Caregiver impact	
Financial/time burden	

Palivizumab (respiratory syncytial virus monoclonal antibody, Synagis©, AstraZeneca, Wilmington, DE) for immunization in infants with CDH and chronic lung disease.[7] A subset of survivors with CDH can have pulmonary infections up to 6–8 times per year, and these patients are more likely to have a larger defect requiring patch repair, high frequency oscillatory ventilation (HFOV) and prolonged artificial ventilation.[17]

Exercise endurance time in children with CDH can also be decreased, particularly in patients who required extracorporeal membrane oxygenation (ECMO) support. When compared to age-matched controls and other patients who required ECMO for respiratory failure, patients with CDH had lower endurance exercise time at age 5, 8, and 12 years.[11]

Neurodevelopmental outcomes

Neurodevelopmental impairment constitutes a significant proportion of morbidity in survivors with CDH, and multiple longitudinal follow-up studies have demonstrated impaired neurological dysfunction.[6,18–21] Laboratory studies demonstrate increasing evidence that patients with CDH are more likely to have neuropathological lesions such as periventricular leukomalacia (PVL), intracranial hemorrhage (ICH), or ventricular enlargement, however, the mechanisms by which these lesions contribute to long-term outcomes are poorly understood.[19]

The frequency and severity of PVL can be proportional to the degree of neonatal prematurity, and this has been attributed to the enhanced vulnerability of premyelinating oligodendrocyte precursor cells to adverse hemodynamics such as hypotension, hypoxia, and acidosis.[22,23] PVL also occurs with increased frequency in patients with CDH compared to controls, suggesting an etiology for central nervous system developmental delay in these survivors.[19] In the perinatal phase, structural brain maturation can be delayed by as much as 1 month behind their gestational age, and up to half of all CDH survivors have magnetic resonance imaging (MRI) evidence for variable degrees of remote and acute ICH.[18] In a cohort of CDH patients with prenatal neuroimaging, many of the postnatal imaging findings were reflective of those seen in critically ill neonates, perhaps more directly related to the treatments and therapies required to treat CDH.[19]

Along with increased disease severity (defect size and liver-up), need for ECMO and underlying genetic comorbidities are associated with poorer neurocognitive outcomes among children with CDH.[20,24,25] Neonates with respiratory failure requiring ECMO demonstrate long-term neurocognitive disability in multiple investigations, and the CDH population fare similarly. Survivors with CDH who require ECMO support are found to have intelligence quotient scores and hand-eye coordination within normative ranges at age 8 years, however, their scores are lower than other patients who required ECMO for alternate diagnoses and also for survivors with CDH who did not require ECMO.[24,26]

Motor function in all children with CDH can be significantly worse than reference peers regardless of ECMO requirement.[24] Motor problems have been reported in 60% of 1-year-old and 73% of 3-year-old CDH children with and without ECMO requirement at birth, and these issues can persist throughout childhood.[6,20,27,28] Subtle cognitive problems in all survivors with CDH are suggested by the fact that 20–40% of children need extra support in regular education.[24] IQ scores reported for childhood and adolescent survivors with CDH range from 99 to 103, in keeping with their age-matched peers, however, intelligence testing alone has not identified those at risk for academic difficulties.[20,29–31]

In patients with CDH who undergo veno-arterial ECMO and have right carotid artery cannulation, revascularization surgery after decannulation has been postulated as a potential method to decrease neurological morbidity from future lateralized cerebrovascular injury. However, carotid repair does carry inherent potential risks of anastomotic rupture, anastomotic stenosis with subsequent plaque formation, cerebrovascular accident, and aneurysm.[32,33] Studies including small series of patients have demonstrated variable success rates with patency after revascularization, and no significant differences in neurological sequelae to date.[32,33] Though initial results after repair show symmetrical blood flow to both sides after unilateral repair without embolic phenomena, patency over time has had mixed results, with some studies demonstrating occlusion of greater than half of all repairs 2 years later.[33–35]

Survivors with CDH are also reported to have significantly more somatic, social, thought and aggression problems at school when compared to controls.[26] It is unclear whether these differences are affected by neonatal ECMO requirement,[21,24] however disease severity and early neurologic dysfunction appear to be predictive of longer-term impairments.[31] Long-term, even non-ECMO treated survivors are at substantial risk for a formal diagnosis of a specific learning disability, attention deficit hyperactivity disorder, autism, developmental disability, or social difficulties.[21,24,31] Perioperative hypocapnia has also been linked to executive dysfunction, behavioral problems, and lowered intelligence in adolescents, linking perinatal hypocapnia-induced cerebral vasoconstriction and consequent local hypoxemia to long-term disabilities.[21,24,36] Perhaps these developmental issues progressively become more apparent as the children increase in age, particularly as they demonstrate the need for placement in specialized classes.[21,24] However, when queried personally, children who survive CDH have unaffected emotional function and report no decline in feelings of competence.[24]

Gastrointestinal morbidities

Gastroesophageal reflux disease (GERD) or some aspect of foregut dysmotility occurs in one-half to nearly all of patients with CDH.[7,9,37] Anatomical mechanisms suspected behind this phenomenon include abnormal orientation of the esophageal hiatus, lack of an angle of His, and distortion of the stomach after herniation into the chest. Long-term reports of GERD morbidity are scarce, however, there have been recent case reports of Barrett's esophagus and even esophageal adenosquamous carcinoma in adult survivors, similar to survivors of esophageal atresia