FOLLOW-UP OF THE SURVIVORS OF CONGENITAL DIAPHRAGMATIC HERNIA

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Abstract

Introduction - Survivors of congenital diaphragmatic hernia have increased with the introduction of new treatment modalities and have been reported to experience ongoing medical morbidity until adulthood.

Aim - To describe the long-term functional impact of congenital diaphragmatic hernia repair on the survivors of a single institution cohort of newborns, over a 14-year period.

Methods – The follow up medical charts of 39 congenital diaphragmatic hernia survivors treated at a tertiary neonatal intensive care unit, from January 1997 to December 2010, were analyzed.

Results - The median age at follow up was 70 (4 – 162) months. Gastrointestinal sequelae were the most common with 12 (30.7%) patients affected by failure to thrive. Chronic lung disease occurred in 5 (12.8%) patients, neurodevelopmental delay in 5 (12.8%), musculoskeletal sequelae in 6 (15.3%), recurrence of hernia in 4 (10.2%) and 2 (7.6%) were deceased.

Conclusion – Congenital diaphragmatic hernia survivors are a group of patients that requires long term periodic follow up in a multidisciplinary setting to provide adequate support and improve their quality of life.

Key words: congenital diaphragmatic hernia; survivors; follow-up; gastrointestinal; neurodevelopmental; musculoskeletal.

INTRODUCTION

Survivors of congenital diaphragmatic hernia (CDH) have increased with the introduction of new treatment modalities, including gentle ventilation with permissive hypercapnea, high frequency ventilation, inhaled nitric oxide, and extracorporeal membrane oxygenation (ECMO) [1-3].

CDH survivors have been reported to experience ongoing medical morbidity [4]. Some institution reports of long-term sequelae include pulmonary and gastrointestinal problems, neurodevelopmental morbidity, orthopaedic disorders, and a less favourable quality of life [4]. Although some single-institution reports have addressed the issue of long-term outcome of CDH survivors, the variability in patient populations, management, and methods for and length of follow-up make if difficult to draw firm conclusions about the quality of life of these patients.

The aim of this review is to describe the long-term functional impact of CDH repair on the survivors of a single institution cohort of newborns over a 14-year period.

METHODS

The follow up medical charts of 39 CDH survivors treated at a tertiary neonatal intensive care unit (NICU), from January 1997 to December 2010, were analyzed. Data retrieved included actual age, weight, length/ height, head circumference, respiratory, cardiovascular, neurological, gastrointestinal and musculoskeletal outcomes. Whenever data seemed incomplete or any doubt arouse in the medical charts analysis the child`s current clinical problems, if any, were assessed on a telephone-based parent medical

history, which addressed nutritional status, cardiopulmonary and gastrointestinal problems, as well as issues with vision, hearing, speech, behaviour, learning, muscle tone and orthopaedic problems.

After discharge from hospital, CDH survivors are cared for in a multidisciplinary follow up. Follow up schedule may change as indicated, but usually includes regular evaluations every three months during the first year of life, every six months during the second year of life, and once a year after two years of age. Anthropometrical indexes are evaluated in all visits and nutritional support by a dietician is indicated when weight is below the fifth percentile, or children have crossed down two major growth percentiles without any other evident aetiology, according to the charts of the National Center for Health Statistics, the growth reference data used in Portugal. Patients that present clinically relevant respiratory problems are accompanied by a paediatric pulmonologist. Since 2006, the respitatory syncitial virus infection immunoprophylaxis with Palivizumab is performed to all CDH survivors. The follow up and treatment of gastro-esophageal reflux disease is performed at the consultation of paediatric surgery. Cardiovascular evaluation and follow up is indicated when the examination is abnormal at discharge from the NICU, or when signs or symptoms of persistent pulmonary hypertension are present, as well as in patients on supplemental oxygen. Neurodevelopmental follow up is performed by a specialized team in symptomatic or patients with previous abnormalities. Brain imaging (ultrasound scan, computed tomography or magnetic resonance) is performed when there are previous anomalies or abnormal neurological signs. All patients are screened for audiological and visual deficits. Orthopaedic evaluation and physiotherapy are performed if indicated.

We considered failure to thrive those children below the fifth percentile for age and those that have crossed down two major growth percentiles without any other evident

morbidity. Diagnosis of gastro-esophageal reflux was done using upper gastrointestinal contrast study. Patients with gastro-esophageal reflux disease were evaluated for esophagitis by endoscopic examination. We considered asthma in those patients presenting with more than three episodes of bronchospasm per year requiring bronchodilator treatment, when excluded other causes of bronchospasm such as allergic rhinitis, sinusitis, laringotracheobronchomalacia or stenosis, chronic exposure to environmental tobacco smoke, viral infections, gastro-esophageal reflux and cystic fibrosis [5]. Chronic lung disease was defined as oxygen requirement for at least six weeks for a transcutaneous saturation of 90% to 95%, along with the use of bronchodilators and inhaled steroids, or the need of respiratory support, and an abnormal chest radiograph. Neurodevelopment is assessed at the neurodevelopmental consultation using the Griffiths Mental Developmental Scale. Cerebral palsy is classified according to the Gross Motor Function Classification System [6].

RESULTS

From a total of 80 newborns with CDH treated at our institution during the considered period, there were 39 (48.7%) survivors, 25 (64%) males and 14 (36%) females. They have presented in the neonatal period a median birth weight of 2810 grams (1335-3725) and a median gestational age of 38 weeks (32-41). Eight (20.5%) were preterm and 20 (51%) had antenatal diagnosis of CDH. None presented any chromosomal or other congenital anomaly. Thirty five patients (90%) had a left side hernia and four patients (10%) had a right side hernia. The median neonatal intensive care unit stay was 21 days (7-167).

Follow-up since 1997 ranged between 1 and 14 years. The median age at follow up was 70 (4 – 162) months. Survivors were not without morbidity. The sequelae found in the follow up are listed in table 1. Seven patients (17.9%) present one sequelae, six patients (15.3%) present two sequelae, three patients (7.6%) present three sequelae, two patients (5.1%) present four sequelae, and three patient (7.5%) presents six, seven and eight sequelae, respectively. In the remaining 10 patients no sequelae were detected. No cases of sensorioneural hearing loss were diagnosed. One patient was deceased by three months old with respiratory failure associated to pneumonia and sepsis. Another patient was deceased by eight months of age, after hernia recurrence repair, need for fundoplication, gastrostomy feeding, chronic lung disease, persistent pulmonary hypertension and multiple respiratory infections.

The ongoing morbidity is more prevalent in those patients under five years of age, when compared to those over five, and this effect is more relevant on respiratory and gastrointestinal morbidity.

The different aspects of therapy used in our CDH survivors are summarized in table 2.

DISCUSSION

More attention is now focused on long-term follow up of CDH survivors. The different centres treating CDH survivors have different follow up schedules and methods of therapy. They also have different protocols for the acute phase treatment at the NICU, and some provide ECMO support. Thus, comparing results of CDH survivors follow up from different centres make it difficult to draw firm conclusions [7,8]. With this idea in

mind we decided to present our own follow up schedule and the different aspects of the used therapy, and allow the readers to compare with their own centre experience. Of course, the proposed follow up schedule and therapies may change for patients requiring strict follow up with closer evaluations, or patents with particular specificities. In addition to long-term pulmonary sequelae in some survivors, follow up studies of infants with CDH have revealed associated non-pulmonary morbidity, including neurocognitive delay, gastroesophageal reflux and other gastrointestinal abnormalities, hearing loss, hernia recurrence, poor growth, and musculoskeletal abnormalities.

Pulmonary outcome

Obstructive symptoms such as bronchospasm or wheezing are frequently reported in CDH survivors, and a high proportion had been diagnosed with asthma [9, 10 - 12]. In our study, obstructive symptoms were the most common respiratory morbidities. These symptoms are perceived to decline with ageing, although abnormalities in pulmonary function tests persist. Most adolescent CDH survivors are healthy and enjoy normal lives. However, in a significant proportion of patients, long-term pulmonary sequelae are detectable and dependent on the severity of lung hypoplasia and the degree of lung injury [9, 10].

CDH survivors suffer from recurrent respiratory tract infections in infancy and early childhood [6, 12]. Recurrent pneumonia or a past history of pneumonia has been found in 26% to 39% of CDH survivors [6].

Chronic lung disease (defined as the need for bronchodilators, diuretics, or oxygen supplementation) has been reported in CDH survivors, but its incidence is unclear [13]. One study reported chronic lung disease in 41% of the survivors [14]. Our experience is limited to five patients. The higher prevalence of chronic lung disease has been

reported in patients requiring ECMO or patch repair of the diaphragmatic defect. The severity of chronic lung disease may require prolonged respiratory support and tracheostomy.

Recurrent herniation usually presents before three years of age. In our study this occurred in four patients, by fourth and fifth month age.

Although most CDH survivors are clinically normal, many of them present subclinical abnormalities in their chest radiographs, lung scintigraphy, and/or pulmonary functions tests. A careful respiratory follow up into adulthood is warranted.

Neurological outcome

A variable, but significant proportion of CDH survivors have neurological sequelae. In our sample, neurological sequelae were detected in seven (17.9%) of the survivors. Several factors are associated with neurodevelopmental outcome in CDH survivors [15]. The need for extracorporeal membrane oxygenation seems related to a poorer neurological outcome. Whether this reflects a more severe primary disease or is a consequence of a more aggressive treatment is unclear, and probably both are true. A prolonged neonatal hospitalization, presumably reflecting the severity of the primary disorder, has been associated with a poorer neurological outcome [16]. A low socio-economic status is another factor to enter in consideration with [9]. Neurodevelopmental outcome is likely to improve with ageing. It is not surprising that initial development may be delayed, but tend to improve with time and with resolution of other organ disorders.

CDH survivors are at high risk of developing sensorioneural hearing loss, due to both the severity of primary disease and the exposure to numerous risk factors, including

ototoxic medications, and prolonged mechanical ventilation with high oxygen tensions. Fortunately none of our CDH survival presents sensorioneural hearing loss.

Neuroimaging abnormalities are relatively frequent in CDH survivors, although their meaning is unclear [5]. In this study, one case of cerebral palsy with cortical atrophy was diagnosed.

Long-term neurological follow up is warranted to early detection of neurological deficits and to provide adequate support.

Gastrointestinal outcome

Gastroesophageal reflux is the most common gastrointestinal sequelae [17]. The incidence of gastroesophageal reflux in CDH survivors is variable between institutions, presumably in relation to the diagnostic method used: pH monitoring, upper gastrointestinal contrast study, or clinical history. Despite its frequency, the pathophysiology of gastroesophageal reflux remains unclear, and many anatomical factors may contribute [18]. Surgical treatment may be indicated in selected patients.

A significant number of CDH survivors show evidence of failure to thrive [2,17]. In our study, this was present in 15.3% (n=6) of the patients. Gastroesophageal reflux disease may be one of the etiologies, but many other factors are implicated in the pathogenesis of growth failure in CDH patients, such as chronic lung disease and oral aversion. Placement of a gastrostomy tube may be required in some patients with growth failure despite aggressive nutritional support.

Other gastrointestinal surgical problems resulting in significant chronic morbidity include intestinal adhesions with obstruction, volvulus secondary to malrotation, intestinal perforation, and ischemia. None of these problems were detected in this study.

The gastrointestinal sequelae were the most prevalent morbidities detected in our CDH survivors.

Musculoskeletal outcome

CDH survivors may suffer from musculoskeletal abnormalities until their growth has stopped, since there is a close relationship between the development of the lung, diaphragm, and the thoracic cage [19]. Chest asymmetry and *pectus* deformity are the most commonly described, followed by vertebral deformities (scoliosis and kyphosis) [13]. Excessive tension on the diaphragmatic repair, the thoracotomy, or the smaller thoracic cavity with smaller lung in the affected side are suggested as possible causes [13].

In conclusion, CDH survivors present ongoing morbidities during infancy and childhood. **This morbidity is more prevalent in the first years of live, and there is some improvement with growth.** CDH survivors are a group of patients that requires long term periodic follow up in a multidisciplinary setting to provide adequate support and improve their quality of life.

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Table 1 – Ongoing morbidity and mortality of the 39 CDH patients discharged from the NICU.

MORBIDITY	TOTAL	PATIENTS UNDER 5 YEARS OF AGE (n=30)	PATIENTS 5 YEARS OF AGE AND OVER (n=9)
RESPIRATORY			
Bronchospasm/ asthma, n (%)	4 (10.2)	3 (10)	1 (11.1)
Recurrent respiratory tract infections, n (%)	3 (7.6)	3 (10)	0
Chronic lung disease, n (%)	5 (12.8)	4 (13.3)	1 (11.1)
Long term (> 6 months) pulmonary hypertension, n (%)	2 (5.1)	2 (6.6)	0
GASTROINTESTINAL			
Gastro-esophageal reflux, n (%)	6 (15.3)	6 (20)	0
Failure to thrive, n (%)	12 (30.7)	10 (33.3)	2 (22.2)
Need for fundoplication, n (%)	2 (5.1)	2 (6.6)	0
Need for gastrostomy, n (%)	2 (5.1)	2 (6.6)	0
NEUROLOGICAL			
Neurodevelopmental delay, n (%)	5 (12.8)	4 (13.3)	1 (11.1)
Cerebral palsy (spastic diplegia, level II *), n (%)	1 (4)	0	1 (11.1)
Strabismus, n (%)	1 (4)	1 (3.3)	0
MUSCULOSKELETAL			
Pectus excavatum, n (%)	6 (15.3)	3 (10)	3 (33.3)
Scoliosis, n (%)	4 (10.2)	3 (10)	1 (11.1)
SURGICAL PROBLEMS			
Recurrence of hernia, n (%)	4 (10.2)	2 (6.6)	2 (22.2)
Patch rejection, n (%)	1 (2.5)	1 (3.3)	0
DECEASED n (%)	2 (7.6)	1 (3.3)	1 (11.1)

* according to the Gross Motor Function Classification System [6]

Table 2 – Different aspects of the therapy used in our CDH survivors.

Morbidity	Therapy
Asthma / Bronchospasm	Reduce environemental exposures; treat co-morbidity conditions as rhinitis, sinusitis and gastro-esophageal reflux; pharmacotherapy is used according to NAEPP guidelines [13]
Recurrent respiratory tract infections	Minimize contacts, nursery > 3 years age; Palivizumab 1st and 2nd Autumns and Winters, annual influenza vaccine > 6 months age, pneumococcal conjugated polysaccharide vaccine (2, 4, 6, 15 months age), purified polysaccharide 23 valent pneumococcal vaccine (PPV23) > 2 years age
Chronic lung disease	Oxygentherapy for saturation 90-95%, bronchodilators, inhaled steroids, nutritional support, kynesitherapy; may need tracheotomy and respiratory support; we usually don't use diuretics
Failure to thrive	Caloric supplementation, nocturnal parenteral nutrition, gavage or gastrostomy for selected cases
Gastro-esophageal reflux	Dietary measures (volumes, thickening of formulas), positioning measures (prone, upright, carried position), procinetic agents, antacids, histamine-2 receptor antagonists (mild-to-moderate reflux esophagitis), proton pump inhibitors (severe and erosive esophagitis); surgery / fundoplication in intractable reflux, particularly those with refractory esophagitis or strictures, and those at risk for significant morbidity from chronic pulmonary disease
Neurodevelopmental delay	Assess presence of psychological risk factors (parents education, mental health, other problems), referral for subspecialty medical services (geneticist, endocrinologist, neurologist), referral for non-medical interventions and developmental promotion
Cerebral palsy	Multidisciplinary approach including physical therapists, speech pathologists, social workers, educators, development psychologists; parents are taught how to work with their child in daily activities and exercises designed to prevent the development of contractures; adaptative equipments (walkers, poles, standing frames, motorized wheelchairs, special feeding devices) surgical soft tissues procedures, rhizotomy procedure, assessment and treatment of lower urinary tract dysfunction ; drugs to treat spasticity including oral dantrolene sodium, benzodiazepines, baclofen, levodopa, carbamazepine, trihexyphenidyl and injection of botulinium toxin, may be used in selected cases.
Strabismus	Ophthalmic specialized correction; the causative types must be distinguished and treated accordingly.
Pectus excavatum	Based on severity of the deformity and extent of physiologic compromise: careful observation; use of physical therapy to address musculoskeletal compromise, and corrective surgery when significant physiologic compromise
Scoliosis	Depends on the extent of the curve and the degree of skeletal maturation. Treatment options include reassurance, observation, bracing, and surgery (spinal fusion)
Recurrence of hernia and patch rejection	Surgery, reconstruction by direct muscle closure if possible; in large defects the use of a reverse *latissimus dorsi* muscle flap

NAEPP – National Asthma Education and Prevention Program