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Long-term morbidity of congenital diaphragmatic hernia: A plea for standardization

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ABSTRACT

Congenital diaphragmatic hernia (CDH) survivors present long-term morbidities in several systems, including the neurodevelopmental, gastrointestinal, pulmonary, and musculoskeletal ones, and CDH long-term sequelae are increasingly being recognized. Due to high co-morbidity, health related quality of life in a significant proportion of CDH patients might be compromised. As a consequence of consciousness on the long-term sequelae of CDH survivors, and their consequences for life, several follow-up programs were brought to life worldwide. In this review, we will summarize the long-term sequelae of CDH survivors, the impact of new treatments, and analyze the consistency of follow-up programs.

Introduction

Congenital diaphragmatic hernia (CDH) is a complex congenital anomaly, where the diaphragmatic defect is only one aspect of a broader, multisystem, developmental defect. CDH patients frequently have associated major congenital anomalies,[1] with their burden of potential long-term morbidities. Additionally, treatment-related factors such as prenatal tracheal occlusion, the need for extracorporeal membrane oxygenation (ECMO), pushed mechanical ventilation, the use of synthetic patches, and minimal access surgery, may further impact on the risk of long-term sequelae. Recently, the CDH Study Group showed that a significant proportion of CDH survivors already have some kind of morbidity at discharge.[2] Over the past decades, the awareness of clinicians on long-term morbidities of patients with congenital anomalies, and their influence on quality of life of patients and families, dramatically increased. This is the case of CDH, upon which long-term morbidity is the focus of a wealth of scientific literature, and several follow-up programs are consequently born worldwide.

In this review, we summarize the long-term sequelae of CDH survivors. In addition, we analyze the impact of new approaches that gained popularity in the last decades and the consistency of follow-up programs for CDH survivors.

Long-term sequelae in CDH survivors

Neurodevelopmental outcomes

Neurodevelopmental impairment is one of the most significant morbidities among CDH survivors. However, the findings across published studies are difficult to compare because of variable study designs and wide range of ages at neurodevelopmental examination. Accordingly, a recent report on from two high-volume European centers identified the need for future multicentric collaborative studies focusing on standardization of postnatal care and long-term follow-up to identify risk factors and thereby reduce neurodevelopmental morbidity.[3]

Neurodevelopmental, neurocognitive and language

Bevilacqua and coworkers found that 1- and 2-year neurodevelopmental outcome of non-ECMO treated CDH survivors fall in the average, although at 2 years of age, 22% have mild to severe neurodevelopmental delay in one or more Bayley-III scales.[4,5] They also found that length of mechanical ventilation directly correlates with 1- and 2-year risk of neurodevelopmental delay, probably being a marker of overall disease severity. Danzer et al.[6] found that, 2-year neurocognitive and psychomotor performance is worse than in the general population, with only 31% of CDH survivors scoring within the average to low average range in cognitive, language, and psychomotor outcome. Intrathoracic liver position, need for patch repair, right-sided CDH, need for ECMO, and O_2 requirement at 30 days of life were risk factors for adverse outcome. The same authors found that at 3 years of age, developmental delays are more in the psychomotor domain than in the neurocognitive one, and that most children with early delays improved in their outcomes. Interestingly, the previously reported risk factors, continued to be associated with persistent motor delays.[7]

Others found that CDH patients develop neurodevelopmental scores significantly below the norm on BSID-III motor, cognitive and language domains at 2 years of age, with prenatal diagnosis, hospital readmission and prolonged need for tube feeds, associated with lower developmental scores at 2 years of age.[8]

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Describing 1- and 3-year language performance in CDH survivors, Leeuwen et al.[9] found similar neurodevelopmental scores at 1 and 2 years of age as compared to controls, with mild delay in expressive language in 21% of patients at 3 years of age.[9] They concluded that CDH is not unavoidably associated with impaired neurodevelopmental outcomes during the first 3 years of life.

In longer follow-up (5 years), Danzer et al.[10] found that the majority of CDH survivors have neurodevelopmental outcomes within the average range, although rates of borderline (17%) and extremely low (17%) IQ scores were significantly higher than in the general population. CDH survivors are also at increased risk for developing emotionally reactive problems. Autism was diagnosed in 11%, which is significantly higher than the general population rate (1.5% at school age).[10] Univariate analysis suggests that prolonged NICU stay, prolonged intubation, tracheostomy placement, pulmonary hypertension, autism, hearing impairment, and developmental delays identified during infancy are associated with worse cognitive outcomes, suggesting that disease severity and early neurological dysfunction predict longer-term impairments.

Despite the cognitive and language development scores at preschool age are normal to mildly delayed, up to 50% of CDH survivors have problems to keep up with the regular education programs and have special educational needs.[11] In a small group of 16 CDH survivors tested at school age, Benjamin et al.[12] found that patch repair, ECMO use, days on ECMO, days of mechanical ventilation, and post-operative use of inhaled nitric oxide were associated with neurocognitive impairment at early school age. Madderom studied 35 children (ECMO: $n = 16$; non-ECMO: $n = 19$) at 8 years of age They found that school performance and competence were not affected.[11] Main intelligence score was higher in the non-ECMO group. Motor problems were evident in 16% of all participants and differed significantly from the norm without differences between treatment groups. CDH survivors had more frequently concentration (68%) and behavioral attention (33%) problems than the control group, without differences between treatment groups.

Motor function and motor delay

Approximately 50% of ECMO graduates acquire normal development in all domains, with severe disabilities occurring in about 13% of patients.[13] Interestingly, 9% of these patients have combined motor and cognitive and/or behavioural impairment.[13] Approximately 40% of CDH patients develop problems in the motor domain at preschool age and 20–30% at school age. Nijhuis et al.[13] also showed that overall psychomotor scores were considerably lower than mental scores, with lowest scores for CDH (−1 SD at 6 and 12 months). The number of associated congenital anomalies as well as duration of admissions and number of surgical interventions proved to be significant determinants of mental and psychomotor outcome,[14] as well as length of mechanical ventilation.[4] In a population of children treated for major congenital anomalies, motor problems were more frequent in children with CDH and EA ($p = 0.001$ and 0.013, respectively).[14] Exercise capacity was lower in this population due to poor exercise performance. So, children with major anatomical anomalies, especially those with CDH and EA, are at risk for delayed motor-function and disturbed exercise capacity.[15] CDH survivors, especially ECMO graduates, have delayed attainment of walking, with abnormalities in tone, delayed motor development and/or motor difficulties in the first few years of life.[16] Davenport et al.[17] found that the mean age at which CDH children first walked was within developmental expectations. However, in this study, the range in ages at which this milestone was reached was broad (10–24 months), and scores on this variable were positively correlated with the length of mechanical ventilation or oxygen supplementation.

Specific risk factors

Several non-CDH related risk factors have been proposed for neurodevelopmental delay also in CDH survivors, including hypocapnia,[18,19] *preterm birthpreterm birth*,[20] the association of acute or chronic *cerebral injury, cerebral injury*,[21,22] a *protracted neonatal hospitalization and oxygen supplementationprotracted neonatal hospitalization and oxygen supplementation*,[23,24] need for ECMO.[6–8,12,25]

Quality of life

Little is known about the impact of long-term health problems on the overall health-related quality of life of these patients. Peetsold et al.[26] found an average mean (SD) total IQ (100.0 (13.2)) and normal visual-motor integration, but significantly lower results for sustained attention (Bourdon-Vos test, 38.8 (11.2) points). Learning difficulties were reported by 30% of parents and health status was not different from the reference population. No significant correlations between test results and severity of CDH were found. Perception of general health is reduced as compared to the reference population, indicating that CDH survivors and their parents believe their health is poor and likely to get worse.[26]

In 21 CDH survivors, Michel et al. report that QoL scores were significantly lower than in controls. Risk factors evaluated were gastro-esophageal reflux at discharge, antenatal diagnosis, length of stay in the PICU, and neuropsychological and respiratory issues. The parents of CDH survivors had considerably worse score in emotional role dimension compared with controls.[27]

Sensorineural hearing loss

In patients with CDH, SNHL has been reported with a variable prevalence, from 0% to 100%.[28,29] Although earlier studies tend to present a higher prevalence of SNHL, in 2015 Amoils and coworkers report a prevalence of SNHL over 50%.[30] Fligor et al.[31] report a 26% overall prevalence of SNHL in ECMO graduates and found that CDH was an independent risk factor for SNHL development. Conversely, van den Hondel et al.[32] found a prevalence of 9% of SNHL, with no difference between ECMO graduates with or without CDH. In CDH survivors, SNHL tends to present as late-onset and progressive. Most studies report normal hearing screenings during neonatal age.[24,29,30,33–36] Multiple factors have been associated with SNHL development, the most frequently being ECMO treatment and its length,[30,31,37,38] length of mechanical ventilation and/or NICU stay,[30,33,34,38,39] loop diuretics treatment and its length,[30,33,37–39] aminoglycosides dose or duration,[31,38,39] pancuronium bromide dose or length.[33,39] Also length of hospital stay,[38,40] need for inhaled nitric oxide,[39] and for patch repair [30] have been associated with an increased risk for SNHL. Overall, CDH patients requiring more aggressive critical intensive care treatments seem at increased risk of SNHL development.

Gastroenterological outcome

CDH survivors may experience several gastroenterological long-term sequelae, including gastroesophageal reflux (GER), failure to thrive (FTT), oral aversion (OA), and small bowel occlusion (SBO).

In infants operated on for CDH, the prevalence of *GER* ranges between 12% and 86%.[41,42] As the prevalence of GER shows a decreasing trend with ageing,[43–48] the inconsistency in age at follow-up between different studies may be responsible, at least in part, for the variability in GER prevalence. In addition, diagnostic criteria used to define GER range from the simple clinical diagnosis to pH-multichannel intraluminal impedance (pH-MII) recordings, adding a further potential methodological bias. In CDH survivors,

several anatomical factors may contribute to GER onset. The mediastinal shift and compression during fetal life, the esophageal kinking at the gastroesophageal junction, the deviation and shortening of the abdominal esophagus, the closure of the diaphragmatic defect under excessive tension, also causing an elevated pressure gradient across the hiatus, and the absence of the peri-hiatal diaphragm, are common in CDH patients. Accordingly, GER disease (GER requiring medical or surgical treatment) and the need for surgery have a higher prevalence in patients with a more severe disease and/or anatomical defect as indicated by liver or stomach in the chest,[44,48–50] prenatal diagnosis of CDH,[51] and need for ECMO or patch closure.[28,44,45,48,49,52,53] In CDH survivors, GER may be asymptomatic. Alternatively, patients may consider the symptoms they experience as a consequence of their primary anomaly, and there may be a mismatch between a relatively silent symptomatology and diagnostic studies such as pH-metry and/or endoscopy. In a study on 26 CDH survivors with a median follow-up of 5 years, Koivusalo et al. found that 5 out of 12 patients with significant GER (symptoms requiring anti-GER surgery, at least moderate esophagitis at endoscopic biopsies, or positive pH-metry) had no or only mild symptoms of GER.[43] Similar findings are reported by Di Pace et al.,[42] who found 12 asymptomatic patients among 26 patients with pathological GER at pH-MII. In a subsequent follow-up study, they found that the prevalence of GER significantly decreases with ageing while the proportion of GER patients that are asymptomatic significantly increases.[48] Recently, Morandi et al.[54] found that 8 out of 12 asymptomatic CDH survivors, who underwent esophagoscopy with endoscopic esophageal biopsies at a mean age of 14 years, had moderate to severe, esophagitis according to the Hetzel-Dent grading system[55] one of which had Barrett's esophagus.[54] The finding of severe esophagitis and/or Barrett's esophagus in asymptomatic CDH patients is an alarming perspective, suggesting the need for long-term endoscopic follow-up programs for CDH survivors. This attitude is further supported by the occurrence of an esophageal adenocarcinoma in a CDH survivor long asymptomatic for GER.[56] Although this may be a stochastic association, the possibility of a reflux induced esophageal damage should be born in mind for long term CDH survivors. In patients with CDH, gastroesophageal reflux may also participate to poorer outcomes, including delayed weaning from mechanical ventilation, longer hospital stay, oral aversion, and failure to thrive. The high prevalence of gastroesophageal reflux and the severity of its sequelae, and the large proportion of patients with CDH requiring antireflux procedures (as many as more than 60% of infants operated on for CDH)[24,52] led some authors to propose preventive fundoplication at the time of CDH repair,[28,49] with controversial results. Some authors found significant benefit of antireflux procedure performed at the time of CDH repair,[57–59] while in the single randomized controlled trial on the issue, Maier et al.[46] found no long-term profit from fundoplication at CDH repair.

FTT is frequent in CDH survivors, with a prevalence ranging from 14% to 63%.[60,61] The wide range of prevalence of FTT may depend on the variability in its definition and age at follow up. For example, FTT has been defined as weight and height <25th percentile,[53] body mass index z-score ≤ 2,[61] weight <3rd percentile,[62] weight <5th percentile,[63] and weight or height <2 z-scores.[64] Also differences in age at follow-up may have an impact on the reported prevalence of FTT. In a prospective longitudinal study on high risk CDH survivors up to the age of 2 years, Valfrè et al.[45] found a progressive improvement of weight and body mass index over time. Conversely, Haliburton et al.[61] found that the prevalence of FTT was the lowest (7%) in the younger age group (5–7 years) and highest (19%) in older age groups (10–17 years). The latter series is a cross-sectional one, and it is possible that only the most severe patients attended the older age follow-up visits, leading to the worsening trend. Accordingly, two studies that followed patients longitudinally and prospectively found a reduction of FTT prevalence with ageing.[24,60] FTT is probably multifactorial, where aspects relating to inadequate caloric intake, due to GER and/or OA (or other feeding difficulties) can have a part in its pathogenesis.[53,62,65] Haliburton et al.[61] recently found that a large proportion of patients, up to 58%, have a resting energy expenditure (REE) higher than expected ($\geq$110%). This higher REE was unrelated to the mass of metabolically active tissues (muscle mass), and the authors suggest that other factors, such as inflammation or work of breathing may be elevating the measured REE. As a consequence of inadequate caloric intake, CDH survivors often require prolonged tube feeding (either nasogastric, gastrostomy, or jejunostomy) to receive calorie-enhaced formulas.[51,63,66] In a subsequent study, Haliburton et al.[65] confirmed the finding of increased REE and found that CDH survivors can achieve optimal weight gain with higher than predicted caloric delivery. The fact that CDH survivors need supra-optimal caloric intake to achieve adequate growth suggests other factors in the pathogenesis of FTT, including ineffective or inappropriate energy expenditure due to reduced oxygenation and/or increased respiratory work. This hypothesis is supported by the association of FTT with need for ECMO,[53] use of high frequency oscillatory ventilation,[62] use of inhaled nitric oxide,[64] vasodilators at discharge,[64] and home O_2,[53,64] all proxy for a pulmonary disease (either hypertension or hypoplasia) that may cause reduced oxygenation capacity and/or increased respiratory work. In addition, Okuyama et al.[67] found a strong correlation between body weight at 1 and 2 years of age and lung ventilation and, especially, perfusion scintigraphy within the first months of life and at follow-up, suggesting that lung function is critical for appropriate growth and that lung scintigraphy may prove helpful in predicting auxological outcome.

OA is a long-term sequela of CDH survivors frustrating for both the families and the clinicians with a reported prevalence ranging from 4%[60] to 25%.[28,53] The families struggle for a normal feeding pattern, often delayed, while clinicians start their challenge with OA definition. The definition of OA is reluctance, avoidance, or fear of eating, drinking, or accepting sensation in or around the mouth. However, it is not always easy to distinguish OA from other types of feeding difficulties such as poor suck-swallowing reflex or immature oral skills. Gastrointestinal disorders that may be associated with discomfort with eating may contribute to the development of OA as suggested by the evidence that patients with GER achieve total energetic requirement per orally significantly later than those without GER[62] and are more likely to require tube feeding at discharge.[51] Muratore et al.[53] report that 25% of their patients had OA and that the duration of ventilation and the need for O_2 at discharge were independent predictors of its development, suggesting that medical traumas such as prolonged ventilation or unpleasant stimuli to the mouths or faces may contribute to the development of OA.

Pulmonary outcome

In CDH patients both lungs have some degree of dysplasia.[68] Therefore, it is not surprising that survivors may present several long-term pulmonary sequelae, both clinical and functional. Although it is common belief that the introduction of new treatment modalities has led to improved survival at the expenses of increased morbidity, this seems not to be the case for pulmonary sequelae.[24,69]

Recurrent respiratory tract infections (RTI) and obstructive symptoms (wheezing/asthma) are the clinical manifestations most frequently reported in CDH survivors. In contemporary series, the prevalence of RTI ranges from below 10% to over 50%.[47,66,70] Valfrè et al.[45] report a trend towards an increase of RTI from 10% at

6 months of age to 23% at 24 months of age. Severity seemed unrelated to the risk of RTI.[45,71] On the other hand, in the series from Koziarkiewicz et al.,[62] RTI were associated with patch repair, need for HFOV, prolonged mechanical ventilation, and lower perfusion at lung scintigraphy. A more severe disease may be associated with higher prevalence of bronchopulmonary dysplasia, which in turn may predispose to an increased risk of RTI. However, Gishler et al.[70] found that CDH survivors with and without bronchopulmonary dysplasia have comparable prevalence of RTI (50% and 60%, respectively).

Obstructive symptoms, defined as asthma, wheezing, and/or the need for bronchodilators or steroids have been reported in a variable proportion of CDH survivors. Ijsselstijn et al.[72] report a prevalence of 23% of wheezing/dispnea at a mean age of 12 years in a cohort of patients treated between 1975 and 1986. In a more recent series of CDH survivors treated between 1987 and 1999 in Amsterdam and Rotterdam, Peetsold and coworkers found a 28% prevalence of asthma.[73] The similar prevalence of obstructive symptoms in the two periods with different treatment strategies suggests that changes in treatment modalities did not influence the development of obstructive symptoms. Spoel et al.[74] recently studied the same cohort of patients reported by Ijsselstijn et al in 1997,[72] at an older age (mean age 27 years). They found that 30% of them had experienced asthma episodes. In younger patients, the prevalence of obstructive symptoms seems lower. Valfrè et al report that at 2 years of age,[45] 12% of CDH survivors had required 3 or more courses/year of steroids or bronchodilators. A similar prevalence of wheezing (14%) is reported by Spoel et al. within the first year of life and by Rocha et al. (10%) at a mean age of 6 years.[47,75] Basek et al.[76] report that 21% of CDH survivors had recurrent (at least 3 episodes/year) wheezing episodes at a mean age of 8 years. Taken together, these data suggest that obstructive symptoms tend to worsen, or become evident, with ageing. The importance of obstructive symptoms is well reflected in pulmonary function tests (PFT) that show obstructive patterns in high proportions of CDH survivors at any age.[45,73,76,77] In all studies, the proportion of patients with abnormal PFT exceeds that of symptomatic patients or receiving bronchodilator medications. It is possible that patients, their families, or physicians underestimate respiratory symptoms, that patients perceive themselves as asymptomatic because that is their “normality”, or they consider symptoms as an inevitable consequence of CDH. The progression of obstructive disorders with ageing is confirmed by pulmonary function tests. Spoel et al.[74] found that airflow obstruction significantly worsened from childhood into adulthood. Obstructive symptoms and abnormal PFT with obstructive patterns may depend upon several causes, including abnormal airways architecture, persistent inflammatory stimulation, and ventilation-induced lung injury. The prevalence of obstructive manifestations in CDH survivors is higher than in the general population but similar to patients without CDH who required similar intensive ventilation as neonates,[74] suggesting that factors not related to CDH itself are responsible for obstructive manifestations. Nose et al.[78] reported 18% anatomic anomalies of the tracheobronchial tree and 38% bronchial hypoplasia in CDH patients. These anomalies may predispose to abnormal PFT. Peetsold et al.[73] found an association of asthma and abnormal PFT with GER and with length of mechanical ventilation. GER may be responsible for persistent inflammatory stimulation to the airways, thereby causing airways hyper-reactivity. The higher prevalence of response to bronchodilators in CDH survivors as compared to healthy controls further supports the hypothesis of increased airways reactivity.[79] On the other hand, prolonged and aggressive ventilation may produce airways injury.[80] Accordingly, CDH survivors ventilated longer than 7 days had significantly lower response to bronchodilators as compared to those ventilated less than 7 days.[73] Finally, it is possible that all these factors act synergistically in the pathogenesis of obstructive complications.

At PFT, CDH survivors also present *lung volumes' abnormalities*. In particular, functional residual capacity and residual volume/total lung capacity ratio (RV/TLC) are significantly higher in CDH survivors as compared to controls or normal values, despite normal or reduced total lung volumes.[72,73,79,81] Such changes may depend upon several reasons, including airway obstruction and hyperinflation, abnormal lung development, abnormal diaphragm function, or a combination of these. Obstructive symptoms/manifestations are frequent in CDH survivors, and may lead to inability to exhale completely. Hyperinflation may also be secondary to emphysematous changes of the hypoplastic lungs. In CDH survivors, histological studies suggest that post-natal lung growth occurs through enlargement of the alveoli, which are reduced in number.[82] Magnetic resonance (MR) studies of lung volumes in CDH survivors have shown that ipsilateral lungs volume is higher than in healthy controls.[83] However, this increase in volume is not associated with increased function, as diffusion capacity of CO_2, corrected for alveolar volume, worsens with ageing.[74] In addition, compliance of the respiratory system has been shown reduced in CDH survivors,[84,85] possibly as a result of hyperdistended hypoplastic lungs. The lung may become hyperinflated in an attempt to fill the empty thorax after reduction of the herniated viscera or hyperinflation may be the result of ventilation-induced injury. Diaphragmatic malfunction may be another factor contributing to the inability to exhale. Abolmaali et al.[83] found marked reduction of diaphragm motion in 12 CDH survivors at a follow-up of at least 6 years, however, the authors do not specify how many patients had primary or patch repair. More recently, in a physiology study of diaphragm function, Kassim et al.[86] found that infants with CDH have a reduced diaphragm contractility associated with a prolonged phrenic nerve conduction time on the affected side. Finally, Healy et al.[87] report a greater degree of hyperinflation in CDH survivors with persistent pulmonary hypertension, suggesting a relationship between disrupted vascular growth and abnormal alveolar development, contributing to airspace overdistension. Accordingly, patients who require ECMO due to a more severe pulmonary hypertension have a higher prevalence of lung hyperinflation.[75,88] However, these patients are also those with a more severe lung hypoplasia, who require longer ventilation and higher airway pressures.[75,87,88] Therefore, the impact of ventilation itself on the development of lung hyperinflation cannot be excluded.

In CDH survivors, pulmonary morbidity is not limited to the airspace, since also the vascular bed may present long-term abnormalities with variable degrees of *persistent or recurrent pulmonary hypertension (PH)*. In infants with CDH, pulmonary arteries and their branches are abnormal.[89] However, limited data are available on changes of vascular abnormalities at long-term and their clinical impact. In a study on 31 CDH survivors with a median age at follow-up of 12 months, Okuyama et al.[67] found that ventilation and perfusion scans on the hernia side significantly improve with ageing, although perfusion remains persistently reduced. These findings further support the concept that the increase in lung volume is rather due to hyperinflation of the hypoplastic lung, than real pulmonary growth. In addition, they found an association between perfusion scan results and long-term morbidity or poor growth. Using serial lung scintigraphies, Pal and Gupta[90] documented a significant pulmonary vascular growth over 6 years of follow-up. Interestingly, patients who required a more intensive treatment, probably due to more severe pulmonary hypoplasia, had a lesser improvement at perfusion scans. Abnormalities in pulmonary blood flow were shown also by MR studies. In 12 asymptomatic CDH survivors, using MR-based cardiac measurements, Abolmaali et al.[83] found increased heart

rate and ventricular ejection fraction and reduced stroke volume, flow, and cross-sectional area in the left pulmonary artery, as compared with normal controls. Previous echocardiography did not show cardiac and/or pulmonary artery pressure abnormalities. The data indicate a persisting vascular hypoplasia in the ipsilateral lung of CDH survivors. The shortened acceleration time in the left pulmonary arteries, in the absence of clinical manifestations, is compatible with a creeping, subclinical, persistent PH. The increased heart rate may be a way to compensate for the reduced stroke volume and flow in the pulmonary vascular bed. These abnormalities are more pronounced in more severe patients, as suggested by the findings that ipsilateral blood volume and flow are significantly reduced in CDH survivors who required ECMO.[91] In a recent study on pulmonary blood flow and vascular resistance in 8 CDH survivors (mean age 17 months) who underwent cardiac catheterization for unspecified clinical indications, Zussman et al.[92] found significantly higher pulmonary artery pressure and vascular resistance and reduced blood flow as compared to controls who underwent cardiac catheterization for PDA closure. Five of these CDH survivors did not have signs of PH on their echocardiogram. These data suggest that a negative echocardiogram alone should not reassure against persistent PH in CDH survivors, especially in those with suspicious clinical manifestations. PH may remain smoldering beneath the ashes for years. High pulmonary vascular resistance alone does not cause severe hypoxemia, unless pulmonary pressure becomes suprasystemic leading to extrapulmonary right-to-left shunt, thereby contributing to long-term morbidity and mortality. Kinsella et al.[93] report on 7 patients who had prolonged or recurrent PH, three of whom died from complications related to PH, at 5, 8, and 19 months of age, respectively. In a study on the causes of late mortality in CDH patients, Burgos et al.[94] found that persistent PH was the cause of death for 2 out of 7 patients who died after 1 year of age. Of note, one patient died at 9 years of age after an asymptomatic period of several years free from medications. We experienced a similar patient (unpublished data) who had a recurrence of PH at 10 years of age, not responsive to maximal medical treatment. At 15 years of age she underwent heart–lung transplant, which was complicated by lung graft rejection after two years and required a re-transplantation. She eventually died at the age of 18 years for progressive pulmonary insufficiency secondary to pneumonia worsened by severe scoliosis and GER. Taken together, these data suggest that PH may subclinically persist, and come to light late in childhood with deleterious effects. Therefore, follow-up should carefully address the issue of persistent PH, finding a reasonable balance between the aggressiveness of investigations and the risks of missing the diagnosis.

Despite all the reported cardio-respiratory morbidities, CDH survivors apparently enjoy normal exercise capacity.[25,73,95–98] Bojanić et al.[99] found a lower aerobic exercise capacity in CDH survivors. However, they also noticed that sedentary CDH survivors fare significantly worse than those who practice sport. The impact of physical activity on exercise capacity of CDH survivors was reported also in other studies.[95,96,98] It may be speculated that sedentary children tend to be less fitted, may be due also to the fear of the parents, than their active peers and perform worse. Regular physical activity is not contra-indicated in CDH survivors[95] and may, on the contrary, be helpful in maintaining or improving their cardiac and pulmonary function.[96,98]

Musculoskeletal outcome

Given the close embryologic relationship between the lungs, thoracic cage and diaphragm, it is reasonable to expect chest wall and thoracic spine deformities in patients with CDH.[100,101]

Chest asymmetry affects up to 50% of CDH survivors, while *scoliosis* and *pectus excavatum* are present in 30% and 20%, respectively.[102,103] Chest wall and spinal deformities develop throughout the entire growth period. Therefore, their true incidence can be defined only when complete development is attained. Since these problems have the potential to influence the quality of life of CDH survivors into adulthood,[101] Jancelewicz et al.[104] suggest to extend long-term follow-up over 7 years of age, ideally up into adulthood. The etiology of musculoskeletal problems can be related to the embryology of CDH, early postnatal therapy (ventilation, nutrition), and also the surgical treatment.[102] Skeletal deformities might be due to an excessive tension of the diaphragmatic repair,[103,105] or to the thoracotomy approach.[101] Experimental studies also suggest that the idiopathic smaller thoracic cavity with smaller lung may have an influence in the development of skeletal abnormalities.[106] Furthermore, several physiological post-surgical factors may contribute to thoracic deformities. Lung hypoplasia may reduce the stimulation to the thoracic expansion. The increased work of breathing may contribute to the development of a pectus abnormality due to more negative intrapleural pressure required to inflate the lungs. A more negative intrathoracic pressure promotes retraction of the chest wall in its most compliant section, the cartilaginous anterior wall.[107] Patients with more severe diaphragmatic defects have a significantly greater risk of pectus deformities, and a trend toward increased scoliosis.[100,102,108] Jancelewicz et al.[109] reported that chest deformity was most common after patch repair at median follow-up of 5 years, suggesting a role for the type of repair on the development of scoliosis. However, they also found that multisystem disease severity, particularly pulmonary failure, seems to increase the risk of chest deformity. In addition, a significant proportion of patients who underwent direct diaphragmatic repair still developed chest abnormalities (21%), downplaying the impact of patch repair.[109] Accordingly, Valfré and coworkers,[45] in a mid-term follow-up study (24 months), found no difference in chest wall deformities between patients with primary and Dacron patch repair at all time points, although, a worsening trend in scoliosis was found for infants who required patch repair (23% vs 7%). Russell and coworkers demonstrated that most of CDH survivors affected by large defects and prospectively followed up, experienced chest wall abnormalities, pectus and/or scoliosis irrespective the type of surgical correction performed (patch repair vs. muscle flap repair).[100] Similarly, Nasr et al.[108] compared chest wall deformities in patients repaired by muscle flap and patch and found no statistical difference across treatment types. In their series, 16% who underwent flap repair developed an abdominal wall defect at the flap donor site but none required surgery. They concluded that both flap and patch repair provide similar long-term results.

Although congenital diaphragmatic hernia-associated chest deformity may be particularly troublesome, as it tends to be asymmetric and progressive, most affected patients have moderate scoliosis with onset that tends to be late in childhood, and often does not require surgical correction at long-term follow-up.[109] Also Chiu et al.[69] report that most of these patients can be managed without surgical intervention and 83% consider themselves healthy.[101] The trend of an increasing prevalence of chest wall deformities with age warrants long-term orthopedic follow-up for early detection, to prevent possible functionally detrimental deformities, and to plan the treatment, if needed.

Surgical outcomes

Recurrent herniation can occur in up to 50% of CDH patients,[110] with re-recurrence in several.[109] Most recurrences occur before 2 years of age.[109,111] Factors associated with recurrent herniation

include disease severity, patch closure of the defect, and minimally access surgery approach,[104,109,111,112] although in experienced hands, also patch repair seems not to be associated with higher rate of recurrence.[113–115] The impact of patch material on the risk of recurrence is still uncertain, with some studies suggesting an increased risk with biomaterials[104,109] and other not supporting these findings.[116,117] Minimal access repair is associated with increased risk of recurrence,[104,109,118] possibly related to the learning curve, to the limited workspace, and to the increased use of a patch.

Small Bowel Obstruction (SBO) occurs in a variable proportion of CDH survivors.[62,104,109,119] The use of a patch seems facilitating the development of SBO,[120] even though other studies failed to show this association.[62,104,109,119] The use of a biosynthetic patch may predispose to the development of SBO, promoting rapid native tissue ingrowth, although no study has shown this association clearly. Hernia recurrence may be another factor predisposing to the development of SBO.[109] SBO may represent a severe long-term complication in CDH survivors. Burgos and coworkers report that SBO were the cause of late death in 3 out of 7 CDH patients who survived to discharge.[94] Of note, although clinical deterioration leading to the exitus occurred suddenly, 2 of them suffered recurrent abdominal manifestations such as abdominal pain, vomiting, and constipation, leading the authors to suggest watchful consideration for abdominal manifestations.

Outcome of new treatment modalities

Prenatal tracheal occlusion

Both natural experiments (congenital high airway obstructive syndrome) and animal experimental models have shown that prenatal tracheal occlusion (TO) leads to increased lung volume due to the accumulation of the naturally produced fluid that cannot pour out.[121] The technique appears to work by preventing the egress of liquid from the lung, increasing airway pressure, causing cellular proliferation, and increasing alveolar airspace and maturation of pulmonary vasculature.[122] Although prenatal TO carries the risk of amniorrhexis and consequent preterm delivery, no serious maternal complications or direct adverse effects on the fetus are reported,[123] and no tracheal damage has been demonstrated in experimental studies.[124] Fetal endoscopic tracheal occlusion (FETO) procedural complications and preterm delivery owing to premature rupture of the membranes have been identified as the most important fetal risks, whereas pulmonary hypoplasia and persistent PH remain the leading cause of death after birth.[125] Because the perinatal morbidity and mortality is decreasing, new adverse effects of FETO are emerging in older patients. Tracheomegaly is a recently recognized sequela of infants with CDH treated with FETO. In 2010, McHugh et al.[124] reported 5 infants who presented with features of respiratory distress shortly after birth and were found to have marked tracheomegaly. The presence of tracheomegaly in survivors who underwent FETO was also found in a cross-sectional study of 7 infants with CDH using CT scans.[126] More recent studies have shown that in some cases, dilation of the airway also involves the main bronchi.[127,128] Studies in animal models have revealed that changes to the tracheal architecture happens also at a microscopic level.[129] Harrison et al.[130] reported a small cohort of patients treated with prenatal TO who had stridor and vocal cord paralysis, two of whom also had tracheomalacia. Other authors did not find an association between the increase in airways' width and short term[131] or long-term tracheomegaly-related respiratory symptoms,[126] and Cortes et al.[24] found no difference in terms of 2 years outcome between CDH survivors who randomly underwent TO or not.

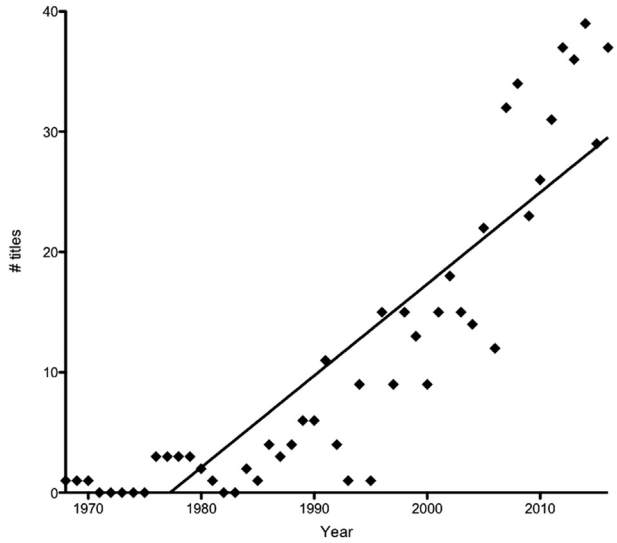

Fig. Titles in Pubmed using the mesh terms "congenital diaphragmatic hernia" and "follow-up". The number of titles published each year progressively and significantly increased from 1967 to 2016 (Pearson $r = 0.8816$, $p < 0.0001$).

Minimal access surgery

With the progression of minimally access surgery (MAS) in the pediatric population, this approach was extended also to CDH patients. The increased risk for recurrence has been already mentioned (see Recurrent herniation). The impact of countermeasures during MAS on recurrence rate is debated but still not defined. Inoue et al.[132] report a significant benefit with the introduction of technical refinements aimed at reducing both intraoperative and post-operative tension in the thorax and to the diaphragm. Conversely, Jancelewicz et al.,[133] reporting the experience of three international groups, found no significant advantage from the implementation of a quality improvement process aimed to reduce recurrences rate in thoracoscopic repaired babies. Recurrences decreased from 50% (in historical TR group) to 39% in the study group but still significantly higher compared with 10% recurrence rate in historical cohort control group, treated with open surgery.

Another aspect raising concern is the hypercapnia, acidosis, and decreased cerebral oxygen saturation associated with thoracoscopy in CDH patients.[134] Inoue et al.[132] have reported that applying specific correctives, pH and pCO_2 were similar between MAS and open repair. Long-term studies are needed to define short- and long-term pros and cons of minimal access approaches in CDH patients, including their neurodevelopmental outcome.

Follow-up programs

The awareness of clinicians on the importance of long-term follow-up of CDH survivors is increased over time. As a result, several follow-up programs were brought to life worldwide. Using "congenital diaphragmatic hernia" and "follow-up" as mesh terms in Pubmed, the search yields 569 titles, with a progressive rise from 1 title in 1969 to 37 titles in 2016 (Pearson $r = 0.8816$, $p < 0.0001$; Figure). In 2014, Tracy and Chen[135] reviewing the literature on medical centers with established follow-up programs for CDH who published follow-up data, report 10 different European and North American centres. In addition to these centers, also the Hospital for Children and Adolescents in Helsinky,[43] Finland, and the University of Heidelberg, Mannheim,[46] in Germany, reported data from their follow-up programs, although not going into details of their organization. Safavi et al report on 12 Canadian

Table
Follow-up programs for CDH survivors at the Hospital for Sick Children in Toronto (Canada), Sophia Children's Hospital in Rotterdam (The Netherlands), and Bambino Gesù Children's Hospital in Rome (Italy). Despite the general attention from a clinical point of view, the programs are difficult to compare owing to the differences in timepoints and tests performed.

	Hospital for sick children Toronto	Sophia children's hospital Rotterdam	Bambino Gesù Chiuldren's Hospital Rome
4 wks	General surgical clinic + CXR	Pediatric surgeon	Pediatric surgeon
3–4 mos	CXR, neonatal FU (AIMS, PFMA-I), hearing test	—	Neonatologist, pediatric surgeon, developmental psychologist (parental emotional assesment)
6 mos	—	Pediatric surgeon, pediatrician, clinical geneticist, cardiologist (ECHO, ECG), PFT (LCI), pH-metry	Neonatologist, pediatric surgeon, clinical geneticist, developmental psychologist (Bayley III + parental emotional assesment), PFT (LCI), hearing test
8 mos	CXR, neonatal FU (AIMS, PFMA-I, CSBS if concerns), cardiologist if PTHN/PDA/PFO	—	—
12 mos	CXR, neonatal FU (AIMS, PFMA-I, CSBS), hearing test	Pediatric surgeon, pediatrician, cardiologist (ECHO, ECG), PFT (LCI), developmental psychologist (Bayley II)	Neonatologist, pediatric surgeon, developmental psychologist (Bayley III+ parental emotional assesment), PFT (LCI), cardiologist (ECHO), upper GI contrast study, pH-metry, hearing test
18 mos	CXR, neonatal FU (Bayley III, M.CHAT, REEL III)	—	Neonatologist, pediatric surgeon, developmental psychologist (parental emotional assessment), PFT (LCI), hearing test, orthopedic surgeon
2 yrs	CXR, cardiologist if no PTHN/PDA/PFO at first assessment	Pediatric surgeon, pediatrician, developmental psychologist (Bayley II-Dutch version, mental scale), physiotherapist (Bayley II, motor scale)	Neonatologist/pediatrician, pediatric surgeon, developmental psychologist (Bayley III + parental emotional assessment), CXR, PFT (LCI), orthopedic, hearing test
3 yrs	Neonatal FU (Bayley III, BRIEF-P, CBCL, Vineland II)	—	Neonatologist/pediatrician, pediatric surgeon, developmental psychologist, orthopedic surgeon, cardiologist, hearing test
5 yrs	CXR, PFT (spirometry), neonatal FU clinic	Pediatric surgeon, pediatrician, psychologist (QoL and social emotional assessment), physiotherapist (movement ABC, Bruce treadmill protocol), PFT (LCI)	Neonatologist/pediatrician, pediatric surgeon, developmental psychologist (Leiter-R), PFT (spirometry and CPET), cardiologist (ECHO), orthopedic surgeon, hearing test
7 yrs	CXR, PFT (spirometry + lung volumes), neonatal FU clinic (if not assessed at 5 years)		—
8 yrs	—	Pediatric surgeon, pediatrician, psychologist (intelligence, neuropsychological assessment, QoL, social emotional assessment), physiotherapist (movement ABC, Bruce treadmill protocol), PFT (spirometry, body pletismography, diffusion capacity, LCI), pH-metry	Neonatologist/pediatrician, pediatric surgeon, developmental psychologist, orthopedic surgeon, hearing test
10 yrs	CXR, PFT (complete with MIPS/MEPS), cardiologist (ECHO, ECG, CT scan, VO_2 exercise test)	—	—
12 yrs	—	Pediatric surgeon, pediatrician, cardiologist (ECHO, ECG), pulmonologist (MRI diaphragm, lungs and vessels), psychologist (neuropsychological assessment, QoL, social-emotional assessment), physiotherapist (movement ABC, Bruce treadmill protocol), PFT (spirometry, body pletismography, diffusion capacity, LCI)	Neonatologist/pediatrician, pediatric surgeon, developmental psychologist, PFT (spirometry and CPET), cardiologist (ECHO), orthopedic, hearing test
15 yrs			Neonatologist/pediatrician, pediatric surgeon, developmental psychologist, PFT (spirometry and CPET), cardiologist, orthopedic, hearing test
17 yrs	Cardiology (ECHO, ECG)	Pediatric surgeon, pediatrician, clinical geneticist, psychologist (neuropsychological assessment, QoL, social-emotional assessment), physiotherapist (movement ABC, maximal exercise test), PFT (spirometry, body pletismography, diffusion capacity, LCI)	Neonatologist/pediatrician, pediatric surgeon, developmental psychologist, PFT (spirometry and CPET), cardiologist, orthopedic, hearing test

Abbreviations: AIMS, Alberta Infant Motor Score; BRIEF-P, Behavior Rating Inventory of Executive Function-Pre-school version; CBCL, Child Behavior Check List; CDH, congenital diaphragmatic hernia; CPET, Cardiopulmonary Exercise Testing; CSBS; Communication and Symbolic Behavior Scale; CT, computed tomography; CXR, chest X-ray; ECG, electrocardiogram; ECHO, echocardiogram; LCI, Lung Clearance Index; LPS, lung perfusion scan; M-CHAT, Modified Checklist for Autism in Toddlers; MIPS/MEPS, Maximal Inspiratory/Expiratory Pressures; mo,month; Movement ABC, Movement Assessment Battery for Children; MRI, magnetic reasonance imaging; PDA, patent ductus arteriosus; PFMA-I, Posture and Fine Movement Assessment first edition; PFO, patent foramen ovale; PFT, pulmonary function test; PHTN, pulmonary hypertension; QoL, quality of life; REEL-III, Receptive Expressive Emergent Language Test third edition; Vineland II, Vineland Adaptive Behavior Scales second edition; VO_2 exercise test, oxygen uptake exercise test; wk, week; yr, year.

centers who hold follow-up programs,[66] and the Japanese CDH study group has developed a long-term follow-up study who reported on several aspects, such as risk factors for hernia recurrence and growth retardation.[112] Given the significance of long-term sequelae in CDH survivors, the Section on Surgery and the Committee on Fetus and Newborn of the American Academy of Pediatrics issued a document to guide post-discharge follow-up of infants with CDH.[136] Despite these guidelines, there is substantial variability among different centers in terms of time points, follow-up duration, and diagnostic tests. By way of example, in the Table, the follow-up programs of three high-volume centers are described.[137] At Sophia Children's Hospital in Rotterdam, the CDH follow-up program involves on a regular basis pediatricians, cardiologists, pediatric surgeons, developmental psychologists, pediatric physiotherapists. Toronto Hospital for Sick Children CDH clinic protocol involves neonatologists, pediatric surgeons,

pulmonologists, gastroenterologists, cardiologists, dieticians, social workers, and a nurse practitioner. Other specialists are involved if necessary. In our Institution, in 2004 we started a dedicated follow-up program for all major congenital anomalies, including CDH. A neonatologist/pediatrician, a pediatric surgeon, a developmental psychologist, and a dedicated nurse see the patients. In addition, other specialists are involved at specific time points (and/or additionally if required). All follow-up programs clearly guarantee the patient from a clinical point of view. However, no-trivial differences exist in terms of time points and diagnostic evaluations performed at each time point. This huge variability is well expressed in the survey from Safavi et al.[66] who analysed the follow-up practices among 16 centers in Canada. They found a high variability in terms of type of follow-up practices, composition of the follow-up team, tests performed, and duration. In particular, in 9 out of 12 centers that responded, follow-up duration was 4 years or less, potentially missing all the morbidities developing thereafter. In addition, in some centers, some specific domains (nutritional outcome, echocardiography, neurodevelopmental outcome) were not explored at all or only in high-risk patients. Consequently, the shortness of follow-up and the lack of close examination in some specific domains may lead to miss potentially severe sequelae. Furthermore, it is conceivable that reports stemming from centers with such different approaches will be difficult to compare.

In conclusion, outcome of CDH survivors may represent a challenge for different reasons. CDH survivors are often asymptomatic, or consider their condition as normal despite the presence of symptoms. This may lead to overlooking important clinical signals and in turn miss or delay the diagnosis and treatment of threatening long-term morbidities. Also new approaches to the severe CDH in fetus and newborn baby leads to new long-term complications such as tracheomegaly and malacia. In addition, problems in detecting long-term sequelae may introduce biases when reporting on the outcomes of CDH survivors. CDH survivors require well-structured long-term follow-up programs to detect, prevent and treat as early as possible the development of their morbidities. Despite the AAP Section on Surgery recommendations,[136] follow-up programs are extremely variable, making it challenging the interpretation of the results and the comparison between reported series. Minimum requirement time points and diagnostic tests should be defined, in order to allow interpretation and comparison among different centers.

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