CONGENITAL DIAPHRAGMATIC HERNIA AND ESOPHAGEAL ATRESIA: THE IMPORTANCE OF RESPIRATORY FOLLOW-UP IN CONGENITAL THORACIC MALFORMATIONS

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[Ernia diaframmatica congenita e atrasia esofagea: l'importanza del follow-up respiratorio nelle malformazioni congenite toraciche]

ABSTRACT

Thoracic congenital malformations may be associated with long-term pulmonary morbidity. Certainly, this is the case for Esophageal Atresia (EA) and Congenital Diaphragmatic Hernia (CDH). These conditions have variable degrees of impaired development of both the airways and the lung vasculature, with a postnatal impact on lung function and bronchial reactivity. Pulmonary complications themselves are frequently associated to non–pulmonary morbidities, including gastrointestinal and orthopaedic complications. These are best recognized in a structured multidisciplinary follow-up clinic and can be actively and precociously managed in order to provide adequate support and improve the quality of life of the patients.

Key words: Esophageal atresia, congenital diaphragmatic hernia, pulmonary function test, respiratory morbidity, Long-term follow-up.

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Introduction

Lung development is a long lasting process, starting during fetal life, and continuing in the early postnatal years. A wide range of pathologies may interfere with normal lung development, some of them leading to permanent sequelae. In this article the long-term pulmonary consequences of two intra-thoracic malformations are discussed, all of them potentially being diagnosed in the early prenatal period[2].

Esophageal Atresia (EA) and Congenital Diaphragmatic Hernia (CDH) are both severe congenital anatomical anomalies requiring neonatal surgery and intensive care treatment. Many important molecules, such as heat shock proteins, are likely involved in early neonatal lung inflammation in case of major congenital malformations requiring surgical repair and prolonged respiratory assistance and their role in these complex metabolic pathways is currently investigated[3,4].

Newborns with major congenital malformations show high incidence of mortality and long term sequelae[5], especially if other risk factors are present such us prematurity, twinning and nosocomial infections[6-13]. Array-CGH (comparative genomic hybridization) analysis has led to the discovery of several submicroscopic genomic variants (duplications and deletions)[14,15], which are responsible for many syndromic conditions with congenital malformations, but none has been clearly associated with EA and CDH till now[18,21].

Continuous progress in medical and surgical neonatal care in recent years had led to improved survival of critical neonates with the consequence of an increase of patients with respiratory and gastrointestinal associated pathologies.

Esophageal atresia

Esophageal atresia is a congenital anomaly of the esophagus which in most cases involves the tra-

chea (78-95%). It is due to an abnormal development of the esophagus from the anterior intestine, occurring between week 4 and 10 of intrauterine life. The overall European prevalence is 2,43 per 10.000 births[22]. Survival of newborns with EA is only possible with surgical correction. Survival rates after surgery in dedicated centres are reported to be around 90% including patients with severe associated anomalies and up to almost 100% in term infants without associated anomalies[23-25]. To achieve these outcomes, as well as a surgical technique, careful preoperative management (early diagnosis, investigation of associated anomalies, suction of the upper pouch, prevention and treatment of gastric and bowel distension) and accurate postoperative care (post-operative analgesia and ventilation, management of trans-anastomotic and chest tube, prevention, early recognition and treatment of complications) are mandatory.

After EA repair in infancy, gastroesophageal reflux (GER), esophageal dismotility and respiratory problems are common. Significant esophageal morbidity associated with EA extends into adulthood. Follow-up for children with EA tends to focus on gastrointestinal pathologic condition[26,28]. Respiratory pathologic conditions, however, are also common and seem equally important. Approximately 10-20% have severe tracheobronchomalacia with airway instability and collapse[29]. In the few adult studies on EA patients, occurrence of respiratory symptoms ranges from 33 to 41%[30]. Recurrent respiratory infections, persistent cough, and wheeze are typical symptoms in childhood[31] and in adolescence[31], with a tendency to improve with age. However, repeated infections, aspiration, and persistent tracheoesophageal fistula may result in irreversible lung damage with bronchiectasis and chronic pulmonary disease[32]. Adults with repaired EA have significantly more respiratory symptoms and infections, as well as more asthma and allergies, than the general populations. Thoracotomy-induced rib fusion and gastroesophageal reflux are the most significant risk factors for the restrictive ventilation defect that occurs in almost half the patients.

Moreover, congenital vertebral defects can lead to restrictive pulmonary function tests (PFTs). In a series of 101 EA adult patients, pulmonary function tests showed obstruction in 21%, restriction in 21% and both in 36% of the patients. Only 20% had normal pulmonary function. Nearly half the patients had bronchial hyperresponsiveness in histamine challenge test, and in 15% it was compatible with asthma. A total of 11% had elevated exhaled nitric oxide levels indicating airway inflammation. Over half the patients with repaired EA are likely to develop scoliosis. Risk for scoliosis is increased 13-folds after repair of EA in relation to that of the general population[32].

Beucher et al. showed that respiratory symptoms are under-detected by physicians and patients, and indicates that PFTs should be systematically performed, early and regularly, even in the absence of clear clinical symptoms. In fact they showed that PFTs and cardiopulmonary stress test were abnormal in many children not complaining of breathing difficulties[33]. Montgomery et al., in an older study, indicated that the functional abnormalities found by PTFs had no impact on exercise tolerance[34]. On the other hand, Gischler et al. suggested a decrease in maximal exercise tolerance[35]. However the clinical symptoms are often minimized, depriving patients of appropriate treatment. Early and prolonged monitoring by multidisciplinary specialists is critical to improve long-term respiratory prognosis[33].

Congenital diaphragmatic hernia

CDH consist of a posterolateral defect of the diaphragm, generally located on the left side, that allows passage of the abdominal viscera into the thorax. The mediastinum is displaced to contralateral side, the lungs are hypoplastic and their arterioles are abnormal causing pulmonary hypertension. The incidence is < 5 in 10.000 live-births[36]. Prenatal diagnosis of CDH now occurs routinely and allows to plan the delivery of high-risk infants in adequate structures or to perform prenatal treatment (reversible fetoscopic tracheal obstruction) in cases with severe lung hypoplasia and grim prognosis. New treatment modalities such as gentle ventilation with permissive hypercapnia, high frequency oscillatory ventilation (HFOV), inhaled nitric oxide (iNO), and extracorporeal membrane oxygenation (ECMO) have improved survival rates in CDH patients[37]. The best hospital series report 80% survival rate but it remains around 50% in population-based series in which abortion, stillbirths and prehospital deaths were considered[38]. As a consequence of the increased survival of more severely affected infants, the long-term outcome of survivors with CDH became an important issue in the management of such patients, because CDH survivors can suffer long-term sequelae, including pulmonary

and gastrointestinal problems, neurodevelopmental morbidity, and orthopaedic disorders[39]. Despite most adolescent CDH survivors are healthy and enjoy normal lifestyles, in a significant portion of patients long-term pulmonary sequelae are detectable and seem to result not only from residual lung hypoplasia with persistent pulmonary hypertension but also from lung injury induced by ventilator support[40]. During gestation, the normal airway develops from the 4th to the 16th week. There is successive branching of bronchi and pulmonary arteries in canalicular (17-27 w.g.) and saccular (27-35 w.g.) stages. Alveolar development, which begins at around 20 weeks of gestational age, is largely completed in childhood by the age of 2-3 years. After this, lung growth mainly occurs by the enlargement of existing alveoli. Thus, any stimulus or insult imposed during fetal or early postnatal life could permanently alter the structure and physiology of the respiratory system with possible long term consequences.

In CDH patients, most have pulmonary hypoplasia which affects both lungs, with a reduced number of airway generations and pulmonary arteries. In CDH survivors, lung hypoplasia persists as demonstrated by ventilation/perfusion radionuclide tests, but the value of V/Q scans in future pulmonary outcome is still a matter of debate. However, more recent unpublished data suggest that children with the most severe V/Q mismatches develop significant limitations in exercise tolerance in middle school[41].

Obstructive symptoms such as bronchospasm or wheezing are frequently reported in CDH survivors, and a high proportion had been diagnosed with asthma. These symptoms are perceived to decline with aging, although abnormalities in pulmonary function tests persist[42]. Actually, CDH survivors may have obstructive, restrictive, and combined pulmonary function anomalies[43]. A decreased compliance of the chest wall may contribute to PFT abnormalities.

Recurrent pneumonia or a past history of pneumonia has been found in 26 to 39% of CDH survivors[44]. Muratore et al. found a high prevalence of viral bronchiolitis in CDH survivors less than 3 years old, despite aggressive antiviral therapy. Since Respiratory Syncitial Virus (RSV) is the most frequent pathogen in these patients, they suggest active RSV prophylaxis in CDH survivors during the period of maximal exposure to the virus[45], even if large multicentre studies are needed to clarify this proposal. Chronic lung disease (CLD) has been reported in CDH survivors, but its incidence is unclear. Van den Hout et al found that 41% had CLD. The higher prevalence of CLD has been reported in patients requiring ECMO or patch repair of the diaphragmatic defect[46].

In conclusion, CDH survivors present ongoing morbidities during infancy and childhood. This morbidity is more prevalent in the first years of life and there is some improvement with growth. Although most CDH survivors are clinically normal, many of them present subclinical abnormalities in their chest radiographs, lung scintigraphy and/or pulmonary function tests. Whether these abnormalities will remain silent for all their lives or will manifest in the event of declining compliance (eg. scoliosis, surgery, or pneumonia), or at a longer follow-up is still unknown[39]. Therefore, 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[47].

Conclusions

Prenatal prediction of postnatal morbidity is a frequently asked question by parents. The potential of successful prediction is limited as many postnatal factors interfering with morbidity cannot be predicted (Fig. 1)[1].

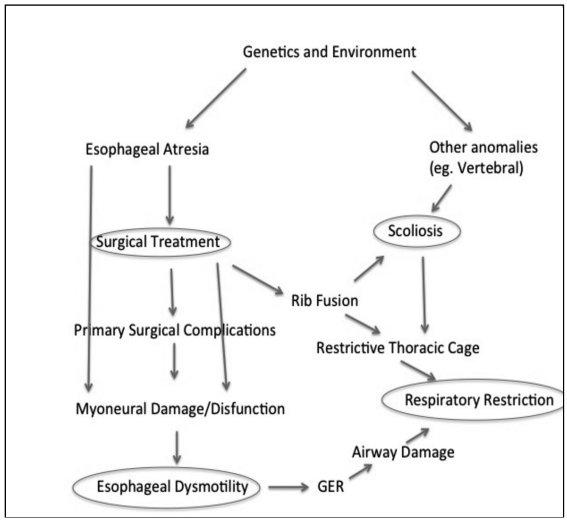

Fig. 1: Flow chart of factors determining long-term outcome of esophageal atresia (Modified from Sistonen SJ et al., 2011).

Measurement of lung function and exercise capacity are helpful for evaluating postnatal lung development[1].

Respiratory symptoms are under-detected by physicians and patients, therefore PFTs should be systematically performed, early and regularly, even in the absence of clear clinical symptoms. Early and prolonged monitoring by multidisciplinary specialist is critical to improve long-term respiratory prognosis.

Multidisciplinary long term follow-up is essential for surgical newborns because of the multi-organ array of morbidities and it has recently been advocated by the American Academy of Pediatrics for CDH[47]. The suggestions provided, however, should be individualized depending on the specific needs of each infant; and the effect of multidisciplinary follow-up clinics needs to be objectivized by appropriate prospective cohort studies.

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