Longitudinal Follow-up of Bronchial Inflammation, Respiratory Symptoms, and Pulmonary Function in Adolescents after Repair of Esophageal Atresia with Tracheoesophageal Fistula

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Objective To characterize symptoms, pulmonary function tests (PFT) and bronchial responsiveness (BR) in adolescents after repaired esophageal atresia with tracheoesophageal fistula and correlate these with endobronchial biopsy findings.

Study design After a primary operation, 31 patients underwent endoscopies and bronchoscopies at the age of <3, 3 to 7, and >7 years. A questionnaire on respiratory and esophageal symptoms was sent to patients at a mean age of 13.7 years (range, 9.7-19.4). The questionnaire was completed by 27 of 31 patients (87%), and 25 of the 31 patients (81%) underwent clinical examination and pulmonary functioning tests. Endobronchial biopsies were analyzed for reticular basement membrane (RBM) thickness and inflammatory cells.

Results The prevalence of current respiratory and esophageal symptoms was 41% and 44%, respectively. "Doctor-diagnosed asthma" was present in 22% of patients. A restrictive and obstructive spirometric defect was observed in 32% and 30% of patients, respectively. Increased bronchial responsiveness, detected in 24% of patients, was weakly associated with current respiratory symptoms and low forced vital capacity. Mean exhaled nitric oxide was within predicted range. RBM thickness increased slightly with age, whereas inflammatory cell counts varied from normal to moderate, with intraindividual variation.

Conclusion Inflammation of the airways in adolescents with a history of tracheoesophageal fistula, even in the presence of atopy, does not lead, in most cases, to the type of chronic inflammation and RBM changes seen in asthma. *(J Pediatr 2008;153:396-401)*

Esophageal atresia (EA) with or without tracheoesophageal fistula (TEF) is a common congenital anomaly, affecting 1 in 2500 individuals.[1] The incidence of associated congenital anomalies ranges from 40% to 57%.[2] Respiratory and gastrointestinal symptoms occur often and can persist lifelong. The etiological factors involved in respiratory problems are thought to be: retained secretions caused by tracheomalacia; aspiration related to impaired esophageal peristalsis and esophageal stricture; recurrence of TEF; or gastroesophageal reflux (GER).[3] Respiratory complications such as recurrent bronchitis, pneumonias, wheezing illnesses, and bronchiectasis are common in patients with repaired EA, but become less frequent with time.[4,5] In an earlier review, patients with symptoms persisting after 15 years were more likely to have had lower respiratory tract illness in early childhood and a history of atopy. Furthermore, weekly episodes of wheezing were present in 33% of patients aged 5 to 10 years and in 15% patients older than 15 years.[6]

Persistent pulmonary function (PF) abnormalities are common in patients with repaired EA both during childhood[5-9] and in adulthood.[4,9,10] Restrictive and obstructive abnormalities are common.[11] Increased bronchial responsiveness (BR), which has been thought to result from chronic subclinical aspiration or other events, rather than atopy, has been shown to be present in 22% to 65% of these children.[5,7,12] It is not known whether the symptoms and reduced PF in this patient group are associated with bronchial

BR	Bronchial responsiveness	PD15FEV1	Provocative dose of histamine producing a decrease of 15% in FEV1
DDA	Doctor-diagnosed asthma	PEF	Peak expiratory flow
EA	Esophageal atresia	PF	Pulmonary function
FE_{NO}	Fractional concentration of exhaled nitric oxide	PFT	Pulmonary function tests
FEV1	Forced expiratory flow in one second	SPT	Skin prick test
FVC	Forced vital capacity	RBM	Reticular basement membrane
GER	Gastroesophageal reflux	TEF	Tracheoesophageal fistula

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inflammation and remodeling (ie, the thickening of the reticular basement membrane [RBM], an irreversible remodeling sign in chronic bronchial asthma).[13]

We tested the hypothesis that, in patients with repaired EA, decreased results on pulmonary functioning tests (PFT) and increased BR during adolescence correlate with early inflammatory changes in the airways. In this longitudinal study, we measured PFT, BR to histamine, and atopy during adolescence. The findings were correlated with current symptoms and with the thickness of RBM and inflammatory cell counts in endobronchial biopsies. We also evaluated the usefulness of a serial bronchoscopic follow-up.

METHODS

Subjects

This study was a longitudinal study consisting of 31 patients with EA and distal TEF. The patients underwent primary anastomosis during 1986 to 1995 in the Hospital for Children and Adolescents, Helsinki University Central Hospital, and they were observed by a pediatric surgeon (H.L.). Patients with EA have a high incidence of long-term esophagitis, gastric metaplasia, and chronic bronchitis, and therefore, it has been the practice in our clinic to perform endoscopic and bronchoscopic follow-up examinations during the preschool and school-age of patients with repaired EA.[14,15]

The study was approved by the Ethics Committee at the Helsinki University Central Hospital, and informed consent was obtained from the patients and their parents before the study.

Study Design

In March 2005, the 31 patients with repaired EA were contacted by means of a letter and invited to participate in the study, which included a clinical examination, PF analyses, and a skin prick test (SPT). The study visits took place from April to June 2005. A questionnaire on asthma and allergy symptoms, validated for use in the International Study of Asthma and Allergies in Childhood, was sent to the patients.[16] Additional questions about pneumonia, dysphagia, GER, and esophagitis were formulated and enclosed. The case notes of all children were reviewed, with particular reference to respiratory and esophageal symptoms and findings. Current symptoms were defined as those present in the 12 months before the study.

Exhaled Nitric Oxide, Pulmonary Function, and Histamine Provocation

As a marker of airway inflammation, the fractional concentration of exhaled nitric oxide (FE_{NO}) was measured according to American Thoracic Society guidelines,[17] by using a chemiluminescence analyzer (Niox, Aerocrine AB, Sweden). The FE_{NO} was considered increased when more than +1.96 SD higher than the height-adjusted reference value.[18] PF was analyzed by using flow volume spirometry (Spiromaster, Medikro Oy, Finland). Ventilatory function was defined as restrictive when forced vital capacity (FVC) was <80% and as obstructive when forced expiratory volume in 1 second (FEV1)/FVC% was <87% of predicted.[19] Bronchial responsiveness to histamine was measured by using a dosimetric bronchial provocation test.[20] The dose producing a fall of 15% in FEV1 (PD15FEV1) was determined from the dose-response curves. According to PD15FEV1, bronchial hyperresponsiveness was categorized as mild (0.41-1.6 mg), moderate (0.11-0.4 mg), or severe (<0.1 mg).[20] Before the PFT, the patients were not allowed to use $\beta 2$-agonists for 24 hours or antihistamines for 5 days. Moreover, the patients had to be free of respiratory infection symptoms during the previous 2 weeks.

Atopy

SPTs were used to test the patients for atopy. Patients who reacted with at least 1 wheal ≥3 mm in diameter to the tested allergens, in the absence of a response to the negative control solution, were defined as being atopic. Standard solutions from ALK (Allergologiska Laboratorium, Copenhagen, Denmark) were used to test for birch, timothy, cat, dog, horse, *Dermatophagoides pteronyssinus*, and *Cladosporium herbarum*. Latex was tested with a solution from Stallergenes (Antony, France).

Bronchoscopy

The bronchoscopies were performed with general anesthesia, by using a rigid 3.5-mm bronchoscope and biopsy forceps (No. 10378L; Karl Storz, GmbH and Co, Tuttingen, Germany). The endobronchial biopsies were taken from the main carina. The severity of tracheomalacia was based on a macroscopical estimation, and according to Filler et al,[21] it was considered severe when the anteroposterior collapse was ≥75% with cough or expiration. Tracheomalacia was considered moderate when the collapse was 50% to 75%, and mild when the collapse was <50%.

Biopsy Processing and Quantification

The 3-μm paraffin sections were stained with the Herovici method as described.[22] Appropriate areas (ie, where the bronchial epithelium was intact) were selected in each sample and sectioned perpendicular to the surface. Ten measurements were taken for RBM thickness in 3 different areas by using a computer-aided image analysis program (Image J; National Institutes of Health, Bethesda, Maryland). The mean value and SD is given for each sample. The number of inflammatory cells was assessed in the following manner. Different inflammatory cells were identified with immunostaining by using these antibodies: T-lymphocytes (CD3), B-lymphocytes (CD20), plasma cells (CD138), eosinophils (ECP), macrophages (CD163), and dendritic cells (CD1a). Neutrophilic leukocytes were identified on the basis of morphology. The number of different inflammatory cells was assessed semiquantitatively by counting the number of positively stained cells per high power field (J.L.). Samples with no positive