Infants Born with Esophageal Atresia with or without Tracheo-Esophageal Fistula: Short- and Long-Term Outcomes

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ABSTRACT: **Background:** The estimated incidence of esophageal atresia (EA) with or without tracheo-esophageal fistula (TEF) is 1:3500 live births. During childhood these patients have various co-morbidities, but the overall quality of life among adults is similar to that of the general population.

Objectives: To evaluate short- and long-term co-morbidities and quality of life among infants born with EA ± TEF at a large single medical center.

Methods: Medical records of 65 children born over a 21 year period were reviewed for short- and long-term medical data. Telephone interviews were conducted with 46 of their parents regarding medical problems and quality of life after home discharge.

Results: The main long-term co-morbidities during the first 2 years of life, 4–6 years of age, and during adolescence (12–16 years) included gastro-esophageal reflux disease (GERD) in 56.5%, 35.8%, and 18.7%, respectively; stridor in 84.8%, 45.2%, and 12.5%, respectively; hyper-reactive airway disease (HRAD) in 43.5%, 35.5%, and 36.5%, respectively; recurrent pneumonia in 43.5%, 32.3%, and 18.8%, respectively; and overall recurrent hospitalizations in 87%, 41.9%, and 25%, respectively. The quality of life was reportedly affected among 100%, 75%, and 33.3% respectively.

Conclusions: Long-term follow-up of patients with EA ± TEF indicates a high burden of co-morbidities during the first 6 years of life, with a gradual decrease in symptoms thereafter. Nevertheless, HRAD continued to impact the daily life of about one-third of the older adolescents, and GERD one-fifth. A long-term multidisciplinary follow-up should be conducted to prevent late onset complications that may affect the quality of life.

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KEY WORDS: esophageal atresia (EA), tracheo-esophageal fistula (TEF), gastro-esophageal reflux disease (GERD), neonates, hyper-reactive airway disease (HRAD)

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Esophageal atresia with or without tracheo-esophageal fistula (EA ± TEF) is a congenital anomaly characterized by interruption of the continuity of the esophagus, sometimes accompanied by a fistula between one of the esophageal stumps and the trachea (TEF). The incidence of EA ± TEF is approximately 1:3500 live births [1,2], and its etiology is usually unknown. EA ± TEF can be an isolated malformation (in about 50% of cases), part of trisomy 13 and trisomy 18, or associated with symptoms such as vertebral, anal, cardiac, tracheal, esophageal, renal, and limb (VACTERL) and coloboma of the eye; heart defects; atresia of the nasal choanae; retardation of growth and/or development; genital and/or urinary abnormalities; and ear abnormalities and deafness (CHARGE) [2,3]. Malformations associated with the presence of EA ± TEF include cardiac anomalies such as ventricular septal defect (VSD), patent ductus arteriosus (PDA), and atrial septal defect (ASD). They also include dextrocardia and other complex malformations, renal malformations (e.g., hydronephrosis, renal dysplasia, polycystic kidney disease), anal atresia, and skeletal deformities (vertebra and long bones) [2].

In less than 10% of cases, EA ± TEF is diagnosed by prenatal ultrasound screening, mostly presented as polyhydramnios [1,4,5]. In most cases, clinical manifestations after birth such, as vomiting, regurgitations, and drooling, lead to postnatal diagnosis. Surgical repair of the atresia and the fistula (if present) generally takes place during the first days of life and can be usually performed in one step.

Survival depends on the presence of other congenital malformations and reaches about 95% among infants with isolated EA ± TEF. It drops to about 20% when associated with major cardiac anomalies or chromosomal abnormalities [6]. During childhood, EA ± TEF patients have various co-morbidities involving the gastrointestinal and respiratory systems as well as growth impairment [6-11]. Nevertheless, the long-term quality of life of adults born with isolated EA ± TEF is reported to be similar to that of the healthy population [7,12,13].

The aim of the current study was to evaluate short- and long-term co-morbidities and the impact on daily life of chil-

dren and adolescents who were born with EA ± TEF at a large single medical center.

PATIENTS AND METHODS

This study was approved by the ethics committee at Sheba Medical Center.

Medical charts were surveyed and reviewed for all neonates born with EA ± TEF who had surgical correction at the Sheba Medical Center (a large tertiary medical center in Israel) during the years 1990–2011. Data were collected in two steps:

1. Perinatal information was gathered through the Sheba Medical Center's archives and medical charts. Recorded data included gender, gestational age, birth weight, small, large, or appropriate for gestational age, delivery mode, single/multiple pregnancy, and post-surgical complications. Early childhood information was obtained from the medical charts of hospital admissions and outpatient clinics, including data regarding hospitalizations, acute and chronic illnesses, surgeries, and growth and development.
2. Long-term data were obtained from the hospital medical charts and through telephone interviews with the parents of the children, whose ages ranged from16 months to 20 years. The interviews were based on a modified quality of life questionnaire that was adjusted to the study population and included five categories:
   a. Medical issues and hospitalizations related to EA ± TEF and invasive procedures during the child's life, specific questions regarding medical problems in the various organ systems (respiratory, gastrointestinal, orthopedic) and feeding and disturbed eating habits
   b. Developmental milestones and school performance
   c. Social skills
   d. Anthropometric data
   e. General perception of their children's quality of life. Questions included, "Does the fact that your child was born with esophageal atresia still affect your child's daily life? If so, in what way?"

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 24 (SPSS, IBM Corp, Armonk, NY, USA). We used the chi-square test for categorical variable and the independent sample *t*-test for numerical variable for the comparisons of prenatal variables between preterm and term infants. In addition, Mantel–Haenszel chi-square was used for trend analysis. A P value < 0.05 was consider statistically significant.

RESULTS

SHORT-TERM OUTCOME

During the study time period 72 infants were diagnosed with EA ± TEF and were hospitalized in the neonatal intensive care unit (NICU) at the Sheba Medical Center. Three infants were excluded due to missing data in the medical charts. The study group consisted of the remaining 69 infants.

Among the mothers of the infants in the study group, the highest incidence of conception (35%) occurred during the winter months (December, January, and February); whereas, the lowest incidence (11%) of conception was found during the spring months (March, April, and May).

Study group characteristics are presented in Table 1. EA ± TEF was significantly more frequent in preterm multiple pregnancies ($P = 0.003$). In addition, the rate of EA ± TEF was found to be higher for in vitro fertilization (IVF) pregnancies that led to preterm deliveries, although not statistically significant ($P = 0.091$).

In four patients, the EA ± TEF was not surgically corrected. Three infants were diagnosed with lethal trisomies (13,18) and the parents decided to withdraw care. The fourth infant died on the first day of life from severe complications of prematurity.

Among the remaining 65 patients, isolated EA ± TEF was found in 21 patients (30.4%). The incidence of VACTERL asso-

Table 1. Study group characteristics

	Total (N=69)	Preterm (n=25)	Term (n=44)	*P* value
Gender (Male)	43 (62.3%)	17 (68.0%)	26 (59.1%)	0.463
Pregnancy				
Spontaneous	43 (62.3%)	15 (60.0%)	28 (63.6%)	0.764
In vitro fertilization	10 (14.5%)	6 (24.0%)	4 (9.1%)	0.091
Multiple pregnancy	10 (14.5%)	8 (32.0%)	2 (4.5%)	0.003
First pregnancy	21 (30.4%)	8 (32.0%)	13 (29.5%)	0.831
Prenatal diagnoses and testing				
Polyhydramnios	43 (62.3%)	16 (64.0%)	27 (61.4%)	0.828
Esophageal atresia suspected during prenatal sonography*	17 (24.6%)	8 (32.0%)	9 (20.5%)	0.285
Prenatal diagnoses using prenatal magnetic resonance imaging	4 (30.7%)	1 (16.7%)	3 (42.8%)	0.343
Birth weight, mean ± standard deviation	2409.48 ± 734.66	1751.04 ± 584.29	2827.02 ± 465.49	‹ 0.001
Gestational age, mean ± standard deviation	37.02 ± 3.11	33.98 ± 2.70	38.92 ± 1.32	‹ 0.001

*Sonographic signs for esophageal atresia include absent fluid-filled stomach, superior esophageal pouch or tracheo-esophageal fistula

ciation was found in 21 patients (30.4%), and EA ± TEF as part of chromosomal syndromes was found in another four cases (two patients with trisomy 18, one with trisomy 13, and one with Down syndrome). In the other 23 infants (33.3%), EA ± TEF was accompanied by a single congenital malformation (VSD, ASD, hydronephrosis, agenesis of one kidney, vertebral anomalies).

For 42/65 of the infants (64.6%) who underwent surgical correction of EA ± TEF and who had data available regarding preoperative and postoperative follow-up, the surgery was performed during the first 3 days of life. Fourteen infants underwent surgery within 4 to 7 days of birth and the nine remaining were operated beyond the first week of life due to low birth weight, long gap, or cardiac issues that needed to be resolved before EA ± TEF correction could be completed. A primary esophageal anastomosis was performed in 50 patients (77%). Another 15 underwent surgical correction in two steps due to a long gap. Of these infants, six underwent gastric pull-up and nine had primary anastomosis with tension. Post-surgical complications included anastomotic leak in 15 patients (23%), pneumothorax in 16 (24.6%), lung atelectasis in 11 (16.9%), chylothorax in 4 (6.1%), recurrent fistulisation in 5 (7.7%), and sepsis in 3 (4.6%). Overall, nine infants (13.8%) who underwent surgical correction died. Causes of mortality included severe cardiac malformation (three infants), sepsis (three infants), complications of prematurity (two infants), and surgical complication (one infant).

LONG-TERM OUTCOME

Fifty-six patients were discharged to home. The parents of 46 were available for long-term follow-up by phone interview. Data from the long-term follow-up are shown in Table 2. The rate of hospitalization was high during the first 2 years of life (87%) and decreased gradually during early childhood to 10% at 16–21 years ($P < 0.001$). The main reasons for hospitalization were stenosis of the esophageal anastomosis and respiratory diseases (mainly bronchiolitis and aspiration pneumonia). Twelve infants (17%) required hospitalization in the intensive care unit during the first 2 years of life.

Stenosis of the esophageal anastomosis was diagnosed in 34 patients (74%). Of them, 22 (65%) underwent at least one endoscopic balloon dilatation, with an average of three dilatations during the first 2 years of life. Food bolus impactions were reported in 36 patients (78%), and a third of them required esophagoscopy to remove the bolus.

Gastro-esophageal reflux disease (GERD) was common during the first 6 years of life, and five of these patients (11%) needed a Nissen fundoplication procedure.

Although parents were instructed to avoid feeding solid foods until the age of 3 years, 60% of the patients were introduced to solid food with no difficulty at an earlier age. Special habits regarding eating solid foods were reported by 34% of the parents, such as drinking large amounts of water with the food or eating very slowly, even at the age of 10 years. Overall, 25% of all patients had behavioral difficulties regarding food and eating (e.g., pickiness, refusal to eat, disturbed eating habits).

The most common respiratory problems were stridor, recurrent pneumonias, asthma or hyper-reactive airway disease (HRAD), and tracheomalacia (clinical or radiological). A high prevalence of delayed growth was reported during infancy, childhood, and even adolescence, followed by marked "catch-up" in most cases during late childhood.

The prevalence of overall complications in the entire study group throughout childhood and adolescence is summarized in Figure 1. While the incidence of GERD, stridor, pneumonia, and weight < 10th percentile decreased significantly as the patients grew, asthma and HRAD remained the leading problem in more than one-third of the patients during adolescence.

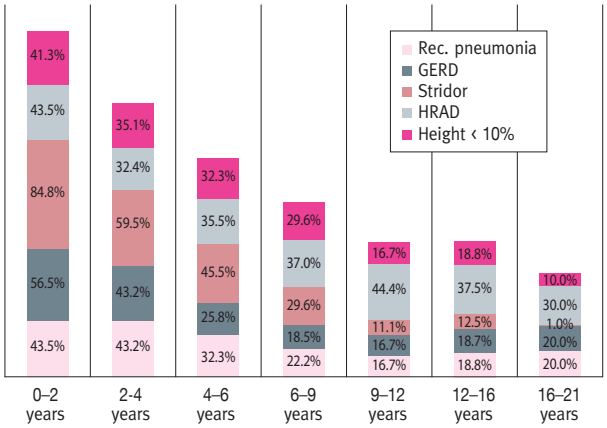
Seven patients (15%) experienced skeletal complications

Table 2. Medical problems by age group: long-term follow-up of children with esophageal atresia

	0–2 years	2–4 years	4–6 years	6–9 years	9–12 years	12–16 years	16–21 years	*P* value
Number of patients	46	37	31	27	18	16	10	
Active illness with hospitalizations	40 (87%)	20 (54.1%)	13 (41.9%)	7 (25.9%)	4 (22.2%)	4 (25%)	1 (10%)	‹ 0.001
Gastro-intestinal complications								
Need for balloon dilatation	22 (47.8%)	4 (10.8%)	2 (6.5%)	1 (3.7%)	1 (5.6%)	1 (6.5%)	0 (0%)	‹ 0.001
GERD	26 (56.5%)	16 (43.2%)	8 (25.8%)	5 (18.5%)	3 (16.7%)	3 (18.7%)	2 (20%)	‹ 0.001
Respiratory complications								
Stridor	39 (84.8%)	22 (59.5%)	14 (45.2%)	8 (29.6%)	2 (11.1%)	2 (12.5%)	0 (0%)	‹ 0.001
Asthma or HRAD	20 (43.5%)	12 (32.4%)	11 (35.5%)	10 (37%)	8 (44.4%)	6 (37.5%)	3 (30%)	0.721
Recurrent pneumonias	20 (43.5%)	16 (43.2%)	10 (32.3%)	6 (22.2%)	3 (16.7%)	3 (18.8%)	2 (20%)	0.004
Growth								
Weight percentile ‹ 10%	20 (43.5%)	15 (40.5%)	13 (41.9%)	9 (33.3%)	5 (27.8%)	5 (31.3%)	1 (10%)	0.037
Height percentile ‹ 10%	19 (41.3%)	13 (35.1%)	10 (32.3%)	8 (29.6%)	3 (16.7%)	3 (18.8%)	1 (10%)	0.008
Summary (non-accumulative calculation)								
Number of patients per age group, at the time of the study	9	6	4	9	2	6	10	
Quality of life affected by esophageal atresia	9 (100%)	5 (83.3%)	3 (75%)	4 (44.4%)	0 (0%)	2 (33.3%)	1 (10%)	0.001

GERD = gastro-esophageal reflux disease, HRAD = hyper-reactive airway disease, MH = Mantel–Haenszel chi-square

Figure 1. Prevalence rates of several common medical problems in children with esophageal atresia, by age



GERD = gastro-esophageal reflux disease, HRAD = hyper-reactive airway disease, rec. pneumonia = recurrent pneumonia

with chest wall deformities and four (9%) had scoliosis, with one case requiring surgical correction.

The parental reports on psychomotor performance included eight patients (17%) with mild motor delay, eleven (24%) with mild cognitive problems, one with severe motor disability, and two diagnosed with autism. The remaining 24 patients were reported to have normal development.

All the parents of infants and children up to 2 years of age reported that EA ± TEF and its co-morbidities affected their child's daily life. Three-quarters of parents of children aged 2–6 years and one-third of parents of teenagers reported that EA ± TEF still affected their child's daily life. The main effect stated was HRAD, which limited social and sport activities. Among older teenagers, parents of 10% reported that their daily quality of life is still affected by EA ± TEF, mainly due to peculiar eating habits.

DISCUSSION

We report a high incidence of respiratory and gastrointestinal complications and repeated hospitalizations among children with EA ± TEF. Symptoms and complications decreased as the children aged. However, many parents of older adolescents reported that their children were still affected by associated co-morbidities, mainly HRAD and GERD.

We found a higher rate of EA ± TEF in preterm multiple pregnancies, as well as a higher rate of EA ± TEF in IVF pregnancies leading to preterm deliveries. These findings are consistent with other reports from the United States [14] and Europe [15].

The higher prematurity rate for our cohort compared to previously reported studies [9] may explain the higher mortality rate, 13.8% vs. about 10% [16]. When other causes of mortality were excluded, the cause of death of four patients (6%) was directly related to EA ± TEF complications. The incidence of peri-operative complications in our study was similar to that previously reported [4,17].

Long-term complications of the gastrointestinal, respiratory, and skeletal systems, as well as growth and developmental outcomes, have been described [5,7-11,18,19]. Anastomotic strictures are common complication. Half of our study population required dilatations, similar to other reports [9,16]. Most of the dilatations were performed during the first 2 years of life and decreased in incidence with age.

The incidence of dysphagia is difficult to assess since it is not reported by the patients directly, but can be deduced by asking specific questions about eating habits and dietary choices. Schier and colleagues [20] reported that 9% of the patients in their study avoided chocolate and sticky candy. A high incidence of eating habit disorders was reported by parents in our cohort, including 34% reporting their child's need to eat slowly or drink large amounts of water with food and 25% reporting peculiar eating habits. From the interviews, it seems that parental attitudes toward their child's illness in general, and toward feeding issues in particular, had a significant effect on the way their children coped. For example, patients whose parents tended to be anxious about feeding were more likely to develop moderate to severe disturbed eating habits.

As in the literature, we found a high incidence (56%) of GERD in patients with EA ± TEF post-surgical correction [4,16,20]. Most of the patients with GERD were treated only medically (usually with an H2 blocker). Only 11% required a Nissen fundoplication procedure, contrasting with 40% reported by Legrand and co-authors [9]. We found the rate of symptomatic GERD to decrease with age, concurrent with previous studies. However, asymptomatic GERD measured by pH-metria was still present in a high percent (up to 50%) of adolescents [10,19,21]. This raises concerns regarding secondary aberrant histologic changes compatible to Barrett's esophagus and even esophageal carcinoma [22].

Aspiration pneumonia, stridor secondary to tracheomalacia, and HRAD were shown to be common clinical manifestations among the cohort of the current study, particularly among young children. Concurring with previous studies [4,16], hospitalization due to recurrent respiratory infections (bronchitis and pneumonia) was common during the first 2 years of life. These infections were usually shown to be secondary to GERD, causing micro-aspirations [4,16,20]. For some of the patients in the current cohort, HRAD due to dysfunction in the central airways persisted until adolescence and adulthood as previously reported [18,19].

A high prevalence of growth retardation was recorded in the first years of our patients' lives. A gradual "catch-up" generally occurred during later childhood (at about the age of 8 years), probably due to a decrease in gastrointestinal and respiratory complications. Other studies have shown that most individu-

als with esophageal atresia reach normal height and weight in adulthood [8,20].

A mild developmental delay during the first years of life was reported by the parents of one-third of the patients. As the incidence of acute illnesses and repeated hospitalizations decreased, the patients achieved normal developmental milestones by school age. Similar to Schier and co-authors [20], we did not find a higher incidence of long-term developmental delay or mental retardation than would be expected in the general population.

The incidence of skeletal problems in our study group was 15%, in contrast to previous studies describing much higher (over 50%) incidence of skeletal deformities among adults born with EA ± TEF [23].

Interviews with parents of children with esophageal atresia, and especially with parents of older patients, showed that the first 2 years of life were difficult and characterized by a high burden of complications and need for medical attention. However, from the age of 6 years most severe respiratory and gastrointestinal problems were attenuated. At older ages (9 years and older) these patients reported leading apparently "normal" lives. Nevertheless, the parents of some older teenagers still reported the persistence of clinical respiratory symptoms and adaptive eating behavior.

Previous studies that assessed quality of life in adults with EA ± TEF found a generally normal quality of life [7,16,21], whereas a later study [24] described a higher medical burden among patients, as in the current study.

Our study has several limitations. First, this is a retrospective study over 21 years. During that period, medical and surgical approaches changed so that the study population was not homogenous. Second, the study is based on data collected from medical files and telephone interviews with parents, raising the possibility of recall bias. Not all patients completed their follow-up at our medical center. Furthermore, the information accessed from the telephone interviews was subjective and reflects parental perceptions of their child's health and well-being over the years. The patients were not seen, nor did they undergo clinical examinations at the time of the interviews. Nevertheless, records from the outpatient clinical files included data on physical examinations. Third, the number of adolescents and young adults in the cohort was small, and there was no comparison to a healthy control group, which limits the interpretations of the results of these age groups.

CONCLUSIONS

In summary, since several medical disciplines (pediatrics, surgery, gastroenterology, dietetics, pulmonology, orthopedics) as well as parental support programs are involved in treatment and medical care, patients with EA ± TEF could benefit from organized multidisciplinary follow-up, as recommended in previous studies [4,9,19,25]. Long-term follow-up of patients with EA ± TEF indicates a high burden of co-morbidities during the first 6 years of life, with a gradual decrease in symptoms afterward. However, HRAD and GERD remain in about one-third of patients throughout adolescence, impacting their quality of life. Long-term multidisciplinary follow-up should be conducted to prevent late onset complications that may affect the quality of life.

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Capsule

An off switch for helminth immunity

Group 2 innate lymphoid cells (ILC2s) are involved in responses to helminths, viruses, and allergens. **Moriyama** and colleagues found that ILC2s interact with the nervous system to modulate helminth immunity. ILC2s from the small intestine expressed the β_2-adrenergic receptor (β_2AR), which normally interacts with the neurotransmitter epinephrine. Inactivating β_2AR resulted in lower helminth burden and more ILC2s, eosinophils, and type 2 cytokine production in mice. Conversely, treatment of helminth-infected mice with a β_2AR agonist enhanced worm burden and reduced proliferation of ILC2s. Thus, β_2AR negatively regulates ILC2-driven protective immunity.

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Eitan Israeli

Capsule

Gut microbiota perturbations in reactive arthritis and postinfectious spondyloarthritis

Reactive arthritis (ReA) is an inflammatory disorder occurring several weeks after gastrointestinal or genitourinary tract infections. HLA-B27 positivity is considered a risk factor, although it is not necessarily predictive of disease incidence. Among nongenetic factors, the intestinal microbiome may play a role in disease susceptibility. **Manasson** and co-authors characterized the gut microbiota and host gene interactions in ReA and postinfectious spondyloarthritis. Subjects with ReA showed no significant differences from controls in gut bacterial richness or diversity. However, there was a significantly higher abundance of *Erwinia* and *Pseudomonas* and an increased prevalence of typical enteropathogens associated with ReA. Subjects with ultrasound evidence of enthesitis were enriched in *Campylobacter*, while subjects with uveitis and radiographic sacroiliitis were enriched in *Erwinia* and unclassified *Ruminococcaceae*, respectively, Both were enriched in *Dialister*. Host genetics, particularly HLA-A24, were associated with differences in gut microbiota diversity irrespective of disease status. The autors identified several co-occurring taxa that were also predictive of HLA–A24 status.

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Eitan Israeli

Capsule

Thyroid hormone inhibits lung fibrosis in mice by improving epithelial mitochondrial function

Thyroid hormone (TH) is critical for the maintenance of cellular homeostasis during stress responses, but its role in lung fibrosis is unknown. **Yu** et al. found that the activity and expression of iodothyronine deiodinase 2 (DIO2), an enzyme that activates TH, were higher in lungs from patients with idiopathic pulmonary fibrosis than in control individuals, and were correlated with disease severity. The authors also found that *Dio2*-knockout mice exhibited enhanced bleomycin-induced lung fibrosis. Aerosolized TH delivery increased survival and resolved fibrosis in two models of pulmonary fibrosis in mice (intratracheal bleomycin and inducible TGF-β1). Sobetirome, a TH mimetic, also blunted bleomycin-induced lung fibrosis. After bleomycin-induced injury, TH promoted mitochondrial biogenesis, improved mitochondrial bioenergetics and attenuated mitochondria-regulated apoptosis in alveolar epithelial cells both in vivo and in vitro. TH did not blunt fibrosis in *Ppargc1a*- or *Pink1*-knockout mice, suggesting dependence on these pathways. The authors concluded that the antifibrotic properties of TH are associated with protection of alveolar epithelial cells and restoration of mitochondrial function and that TH may thus represent a potential therapy for pulmonary fibrosis.

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Eitan Israeli