Original article

Esophageal atresia: long-term interdisciplinary follow-up

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Abstract

Background: We provide protocolized interdisciplinary follow-up to babies born with Esophageal Atresia (EA). There are few reports in Argentina about follow-up of EA patients.

Objective: To describe outcomes in follow-up of EA patients at 1, 3 and 6 years old and to compare outcomes at age 1 with those at age 6.

Methods: Prospective, longitudinal, analytic study of the cohort of babies born with EA, admitted to the follow-up program from 11/01/03 to 10/31/14. Follow-up includes: growth (weight > 10th centile, WHO), neurology-psychomotor development, audiology, vision, genetic, mental health, surgical reintervention, phonostomatology, language, pulmonology, re-hospitalization for clinical causes, lost to follow-up. Outcomes were described at age 1, 3 and 6. We included all EA patients who had reached age 1 at the start of this study.

Results: 27 babies were admitted; 30% had long-gap EA; 18% presented VACTERL association; 23 children met inclusion criteria. Genetics was assessed in 18 newborns (78%); a chromosomal map was performed in 11 babies; 3 had an abnormal karyotype. Mental health: 5/14 of the assessed children showed problems. Phonostomatology: 11 newborns checked (6 required treatment, 4 recovered at age 1). Pulmonologist evaluated 18 babies (7 with recurrent wheezing, 6 with moderate tracheomalacia). Gastroenterology and endoscopy: 80% presented gastroesophageal reflux (GER) grade 3-4, and 50% showed a pathologic pHmetry. Lost to follow-up: age 1, 2 (8%); age 3, 3 (17%); age 6, 3 (23%). Normal outcomes observed are the following. Age 1 – growth: 81%; neurologic-psychomotor developmental index (NPDI): 76%; audiology: 95%; vision: 85%; language: 62%; re-hospitalization for clinical causes: 38%; surgical reinterventions: 47%. Age 3 – growth: 78%; NPDI: 50%; audiology: 93%; vision: 93%; language: 43%; re-hospitalization: 35%; surgical reinterventions: 14%. Age 6 – growth: 50%; NPDI: 30%; audiology: 90%; vision: 40%; language: 50%; re-hospitalization for clinical causes: 0; surgical reinterventions: 7%.

Conclusions: Patients with EA are at risk for long-term morbidity and impairments. Long-term follow-up should be warranted for them.

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Introduction

Esophageal Atresia (EA) with or without tracheoesophageal fistula is a complex congenital disease that affects the tracheoesophageal region of the foregut [1]. It is the most common anatomical congenital anomaly (CA) of the esophagus and is one of the most common surgically correctable life-threatening CAs. It has an overall incidence of 1 in 2,500 to 1 in 3,000 live newborns [2]. There is a gap of a variable length between a blind upper esophageal pouch with or without a tracheoesophageal fistula, and the lower part of the esophagus with or without a tracheoesophageal fistula, too. There have been several classifications of EA published, based on different criteria [3-7]. It is important to remember that the EA is a spectrum of anomalies into the embryology of foregut.

More than a half of these babies present with associated malformations in the vertebral column and the spinal cord, heart, other parts of gastrointestinal tract, genitourinary system and limbs. These associations constitute different syndromes: VACTERL, CHARGE, etc. [1, 3, 5].

Babies with surgical illnesses undergo anesthesia, NICU stay, nosocomial infections, postnatal malnutrition which highten the risk for developing long-term sequelae. EA is a CA recognized as responsible for long-term morbidity, especially abnormal lung and gastrointestinal tract functioning, growth and reinterventions. It has been reported that babies born with EA are at risk for neurodevelopmental delay and psychomotor impairment. The etiology is unknown but it seems that multiple causes are involved [1-4]. These children should be assessed on an interdisciplinary basis in order to treat the progressive dysphagia, to help in the adjustment to the multiple surgical reoperations, and to check the language skills development.

The Argentine National Register for Congenital Anomalies (RENAC) published in 2013 a prevalence for EA of 3.6 (2.9-4.4) / 10,000 live births, and a total number of 101 babies reported with this malformation in the same year [8, 9].

The Pedro de Elizalde Children's Hospital, our tertiary care Pediatric Hospital, is one of the three referral centres for babies born with major anatomical CAs requiring surgical correction in the metropolitan area of the City of Buenos Aires, Argentina. We provide interdisciplinary, structured follow-up to babies discharged from the NICU, up to 7 years old; among them, the newborns with EA represent 14% of the population. There are few reports about the long-term outcomes of babies born with EA, on an extensive interdisciplinary basis. We have previously reported that newborns with anatomical CAs, undergoing surgery during neonatal period, show high frequency of neurodevelopmental delay, and children born with EA are not an exception [10]. We have also previously reported our results in the follow-up of babies with gastroschisis describing the outcomes at 1, 3 and 6 years of age [11].

The aim of our study is to report the long-term outcomes from our interdisciplinary follow-up program, in a cohort of babies born with EA.

Objectives

1. To determine the outcomes in the interdisciplinary follow-up in the cohort of babies born with EA, in the following areas: genetics, mental health, phonostomatology, pulmonology, gastroenterology, growth, neurologic-psychomotor developmental index (NPDI), hearing, vision, language, re-hospitalization for clinical causes, surgical reoperation, and lost to follow-up.
2. To compare qualitative outcomes for growth, NPDI and language developmental skills (LDS) at age 1 and 6 years.

Study design and methods

This is a prospective, longitudinal study, performed in the setting of the Follow-Up Program for High Risk Newborns, Health Promotion and Protection Division, Children's Hospital Pedro de Elizalde, in Buenos Aires, Argentina.

It includes the cohort of babies born with EA seen in the follow-up program, who reached the first year of life at the start of this study.

The follow-up program is run by an interdisciplinary team (**Tab. 1**). All babies discharged from the NICU with birth weight (BW) ≤ 1,500 grams and/or history of surgical correction of CAs, and/or those who had been on mechanical ventilation for any reason are assessed in a protocolized, systematic, interdisciplinary approach.

For surgical purposes, we use a simplified classification for EA:
1. EA without tracheoesophageal fistula;
2. EA with proximal tracheoesophageal fistula;
3. EA with distal tracheoesophageal fistula;
4. EA with double, proximal and distal, tracheoesophageal fistula.

Table 1. Interdisciplinary team.

Team member	Role
Neurodevelopmental Pediatrician/ Neonatologist (2)	Growth/neurodevelopment surveillance. Coordination of interdisciplinary evaluation
Nurses (2)	Visits to families during NICU stay, family education, ostomy care, health promotion follow-up
Surgeons (2)	Follow-up care of surgical issues. Timing of special studies. Communication with other surgical subspecialties
Geneticist (1)	Examination of patients with a major congenital anomaly and eventually chromosomal analysis performance (i.e. > 2 major congenital anomalies)
Psychologists (2)	Mental health promotion and support for children and families
Therapists (2)	Assessment during NICU stay, decision making about early intervention program
Pulmonologist (1)	Surveillance of respiratory tract integrity and function
Stomatologists (2)	Assessment of suck-swallow skills and treatment from NICU stay, continuing during follow-up
Language Speech Therapist (1)	Evaluation of receptive-comprehensive language from 6 months old every 6 months up to 7 years old
Audiologist/ENT (2)	Assessment of hearing according to AAP hearing follow-up recommendations
Neurologist (1)	Surveillance of neurological status
Ophtalmologist (1)	Assessment according to recommendations for visual screening

The variables collected included: gestational age (GA), BW, days on mechanical ventilation, intrauterine growth retardation (IUGR), type of EA, surgical management (end-to-end esophageal anastomosis; gastrostomy: yes/no). Results are described at age 1, 3 and 6 years, and they are reported as normal/abnormal for genetics (reported once), mental health, phonostomatology, pulmonology, growth (normal: weight > 10th centile, WHO), NPDI, hearing, vision, and language, lost to follow-up, re-hospitalization for clinical causes, and surgical reoperation (reported as "yes/no"). At 6 years of age we considered: mainstream education/need for special education.

The phonostomatologist is a phonoaudiologist with a post-degree specialization whose objective is the evaluation of swallow function for oral feeding skills (suck-swallow-sip-chew-phonoarticulation) and related to respiratory function. The phonostomatologist assesses and intervenes during the stay in the NICU immediately after the baby is weaned from the ventilator (5-7 days post-surgery) and with the first enteral feedings. The evaluation includes a clinical and morphological examination and, if necessary, a video-deglutition radiologic study is performed. During follow-up the assessment includes surveillance of feeding technique regarding posture (body, head-neck) speed and rhythm of ingestion and the consistency/texture of the feeds. The introduction of solid should be progressive. If the baby has an esophagostomy, the phonostomatologist will only work stimulating orofacial muscles and, in cases with tracheostomy, there will be an evaluation of swallow capability. Re-evaluation of clinical condition is done in every session in order to assess the ongoing feeding skills development.

Surveillance of neurodevelopmental status

We administered two batteries for NPDI screening:
a. Capute Scale Clinical Adaptive Test/Clinical Auditory Milestone Scale (CAT/CLAMS) for children less than 3 years old. This test focuses on the skills to solve visomotors problems (CAT) and the receptive and expressive language skills through an interview and questions designed for parents. The results are expressed in a 0-100 score and qualitatively as "normal/suspect/delayed" [12]. Borderline ("suspect") result at CAT/CLAMS is considered as abnormal at McNemar's test evaluation;

b. PRUNAPE (Argentine Screening Test) which is an Argentine instrument designed for early detection of unapparent neurodevelopmental problems for children under 6 years old. The battery consists of 69 developmental milestones examining fine and gross motor function, language skills and social area. The results are expressed as "pass/fail" [13].

In this report we expressed the results for NPDI with both tests as "normal/abnormal".

Data were obtained from the charts of each patient and entered in a Microsoft® Excel® chart (Microsoft® Office® Professional XP, Redmond, Washington, USA), and they were described through simple frequency and proportions. Statistical analysis was performed with Stata® version 8.0 (StataStatistica Software, Release 8.0, Stata Corp College Station, TX; 2003). The matched-pairs analysis was performed with the McNemar's test.

The Medical Ethical Review Board approved this study, and parental informed consent was obtained for all subjects prior to enrollment.

Results

Twenty seven babies born with EA diagnosis were admitted to the follow-up program; 4 died before 1 year old (all of them with long-gap EA); 23 children met inclusion criteria and they were assessed at age 1; 17 children of this cohort reached 3 years old, and were evaluated at this age and out of them, 13 children were examined at 6 years old.

Tab. 2 shows the perinatal characteristics of the subjects, and **Tab. 3** the characteristics of the EA and surgical resolution.

The geneticist examined 18/23 babies; a chromosomal analysis was performed on 11 newborns: 3 (16%) had an abnormal result (1 no clinical significance, 1 had 21 trisomy and 1 had Edwards syndrome). Mental health followed 14 families, the remaining parents declined the evaluation: in 4 cases (28.5%) there were family dysfunction and attachment problems; 1 child was referred for psychiatric evaluation.

The phonostomatologist assisted 11/23 babies (48%): 2 (18%) had a normal evaluation, 6 (54%) showed abnormal suck-swallow patterns, and were put on treatment; at age 1, 4 (66%) achieved normal eating skills, and 3 had a gastrostomy tube placed for feeding.

Pulmonologist examined 18 babies (5 declined the evaluation); 5 (27%) showed normal lung function,

Table 2. Perinatal characteristics (n = 23 babies).

	Mean (SD)	Median (IQR)	Min-Max
GA (weeks) [a]	38.3 (± 1.6)	38 (37-40)	34.2-41
BW (grams) [b]	2,917 (± 440)	3,015 (2,605-3,245)	1,950-3,660
Mechanical ventilation (days)	8.6 (± 7.5)	7 (4-8)	3-35
TPN (days)	11.5 (± 6)	11 (7-13)	3-38
LOS (days)	53.4 (± 41)	34 (29-68)	16-142

IQR: interquartile range; TPN: Total Parenteral Nutrition; LOS: Length of Stay.
[a]Prematurity rate: 19% (n = 4); [b]Intrauterine Growth Retardation: 19% (n = 4).

Table 3. Type of Esophageal Atresia (EA) and surgical resolution (n = 23).

		n (%)
Type of defect [a]	**Type 1 EA**	3 (13)
	Type 3 EA	20 (87)
Surgical technique	**Primary end-to-end anastomosis**	19 (82.6)
	Delayed anastomosis/ gastrostomy [b]	8 (34.8)

EA: Esophageal Atresia.
[a]8 cases (34.8%) long-gap EA – 5 cases (21.7%) VACTERL association; [b]other ostomies: 9 (39.1%) – 6 children (26.1%) with ≥ 2 ostomies.

7 (38%) showed recurrent wheezing, and 6 (33%) moderate tracheomalacia.

Gastroenterology and endoscopy: 80% of the population showed gastroesophageal reflux (GER) grade 3-4 according to the endoscopic modified classification by Savary-Miller, and 50% showed an abnormal esophageal pH monitoring.

McNemar's test results show that out of 6 patients with normal growth at age 1, 5 continued within normality at age 6. 1 patient with abnormal growth at age 1, showed abnormal growth at age 6 (p-value = 0.32), while out of 4 patients with normal LDS at age 1, 1 showed abnormal LDS at age 6 (p-value = 0.08), and out of 7 patients with normal NPDI scores at age 1, 3 showed normal NPDI score at age 6 (p-value = 0.04).

Tab. 4 shows the results of the protocolized interdisciplinary evaluations performed at 1, 3 and 6 years of age.

Table 4. Interdisciplinary follow-up.

	Age 1 n (%)	Age 3 n (%)	Age 6 n (%)
n	23	17	13
Lost to follow-up	2 (8.70)	3 (17.65)	3 (23.08)
Patients assessed	21	14	10
Growth > 10th centile	17 (80.95)	11 (78.57)	5 (50)
Normal NPDI	16 (76.19)[a]	7 (50)[b]	3 (30)[c]
Normal AUD	20 (95.24)[d]	13 (92.86)[d]	9 (90)[d]
Normal vision [e]	18 (85.71)	13 (92.86)	4 (40)
Normal language	13 (61.90)[f]	6 (42.86)[g]	5 (50)[h]
Re-hospitalization [i]	8 (38.10)	5 (35.71)	0
Surgical reoperation [j]	10 (47.62)	2 (14.29)	1 (10)

NPDI: Neurologic-Psychomotor Developmental Index; AUD: audiology.
[a] 2 cerebral palsy (CP); 2 mild motor impairment (MMI); 2 neurologic-psychomotor developmental (NPD) delay; 1 with seizures.
[b] 2 CP; 1 MMI; 5 NPD delay.
[c] 2 special school.
[d] 1 sensorineural hearing loss (SNHL).
[e] 2 astigmatism; 1 coloboma.
[f] 7 expressive language disorder (ELD), 1 language comprehension disorder (LCD).
[g] 8 ELD, 1 LCD.
[h] 4 ELD.
[i] 7 > 1 re-hospitalization.
[j] 8 ≥ 2 surgical reoperation.

Discussion

EA itself and its surgical repair are cause of motility changes in the esophagus, GER and its complications. There is a recognized strong association between the severity of GER and the presence of respiratory illness. One third of the babies with a history of surgical repair of EA will have respiratory symptoms in adolescence and adulthood; there are reports about respiratory function abnormalities which could obey to different causes [14]. A high risk for scoliosis has been reported in patients with a history of surgical repair of EA. Long-term nutritional assessment is a very important issue in these children, and their growth is significantly different from the normal population [15, 16]. More than 25% of the babies will develop a stenosis in the surgical scar of the esophagus, and a high proportion will require further surgical reoperation. The surgical repair in the neonatal period, the associated malformations, and the predisposition to respiratory and gastrointestinal morbidity, including preneoplasic lesions (associated to severe GER) [17], should arise concerns about other health issues, such

as neurodevelopmental delay, speech language pathology, risk of hypoacusia.

Gischler et al. performed an interdisciplinary follow-up program in children born with CAs, up to 2 years old, reporting several health problems in those with EA [18].

However, there are no comprehensive inter-disciplinary follow-up clinics for the prospective assessment of these children in order to provide timely screening, surveillance, diagnosis and treatment of long-term complications. In our interdisciplinary follow-up groups, the pediatric sub-specialties and other disciplines are required to perform an extensive and long-term surveillance of children born with CAs admitted to the program.

Our results show a very good adherence to the follow-up; at age 1 and 3 the lost to follow-up is below the percentages considered as acceptable by the guidelines for follow-up published by the Committee of the Fetus and Newborn of the American Academy of Pediatrics (AAP). At 6 years old we have a lost to follow-up slightly beyond the limit of 20% stated by the AAP publication, so we consider that our results are representative of our population [19]. We found reports of lost to follow-up as high as 25% [18].

The evaluation of the geneticist is superimposed with the stay in the NICU, because we strongly suggest to neonatologists that this assessment should be done as soon as possible. Our data on genetic issues are similar to those published by other authors [9, 10]. Our results show a high prevalence of babies with long-gap EA; we speculate that this is related to the complex babies transferred to a surgical tertiary care referral center, as is our hospital.

We provide mental health assistance with a preventive scope to every child admitted to our follow-up program, but this aspect is especially necessary in children born with EA. Our results resemble those of other authors regarding the prevalence of mental retardation and motor impairment. Kubota et al. reported that mental retardation was apparent in 25% of children born with EA and behavior disturbances in 35% of the same population. They also reported about the effect on maternal stress when giving birth to a child with a major CA and the impact on attachment between mother and baby; they highlight the importance of taking in consideration the surgical stresses that the baby will suffer, until the malformation is completely resolved [20]. Caplan et al., in the Sainte-Justine University Hospital in Montreal,

observed an increased risk for postraumatic stress disorder in the parents of these children as long as three years after the birth of their child [21].

Regarding phonostomatology, our experience reflects a major impairment in the feeding function with an overall good outcome if the variables gestational age, weight, associated anomalies and the neural system integrity, are good or well preserved. Other factors to take into account are the period of intubation and mechanical ventilation because if they are prolonged the vocal cords and the glottis will be impaired to function during the suck-swallow process [15, 22, 23].

Pulmonologist should assess every child born with EA because this is a malformation extended to the tracheobronchial system. Our results are similar to those reported by other authors. Delacourt et al. [24] reported that children with EA had a high risk for long-term impaired lung function even if GER or an abnormal esophageal pH monitoring are not associated, and that respiratory symptoms can persist until adolescence and adulthood. Tracheomalacia represents another contributing factor to respiratory symptoms. We found moderate tracheomalacia in a lesser proportion than reported by Delacourt. Regarding respiratory endoscopic aspects, our results on recurrent tracheoesophageal fistula resemble those published in the pediatric endoscopy and surgical literature. We successfully managed all the cases with endoscopic chemical cautery; and we have not surgical repairs in these patients. Connor et al. published a systematic review and meta-analysis outlining the prevalence of common long-term problems associated with EA repair in patients older than 10 years of age [17]. Regarding gastroenterologic aspects, the pharyngeal and esophageal phases are abnormal in all patients. Whatever the cause, congenital or acquired, it brings with it several problems, mainly the GER. We have a high percentage of it although within normal range. Antireflux medication, including gastric acid suppression, was successful in only about half of the cases. We performed antireflux operations in patients with repaired EA when there seemed to be no other clinical alternative. The question remains whether adults with repaired EA as an infant should have a higher incidence of Barrett's esophagitis, esophageal cancer or squamous cell carcinoma [14].

Growth is a major concern in EA patients, as a consequence, partly, of feeding impairment. Our results in this aspect resemble those of Spoel et al. [25] who reported the outcomes of follow-up of respiratory and growth variables up to 2 years of age, in children who received different surgical approaches. Despite the differences between the two groups analyzed by them, they observed an overall deficit in growth compared with normal population. GER, abnormal esophageal pH monitoring and frequent respiratory tract infections contribute to the failure to thrive in EA patients. Long-gap EA and the gastrostomy tube fed children represent a major challenge for nutritionists and the follow-up team, not only because of growth issues. Our goal is to rehabilitate them as soon as possible so they can achieve normal feeding patterns which will be the base for LDS.

The neurologist of our team assesses babies prior to discharge, and therapists perform an evaluation as well. A brain ultrasound is also performed, and according to the results of this screening, the post discharge visits are protocolized. When admitted to follow-up program, the babies have protocolized examinations with the pediatrician specialized in neurodevelopment. This assessment leads to the decision to refer or not to early intervention services. Our results show that there are suboptimal outcomes at 1, 3 and 6 years of age. A quarter of our population are born late preterm, with IUGR, without a normal suck-swallow pattern since the intrauterine life (and inadequate during a variable time postnatally), prolonged in-hospital length of stay, anesthesia and surgical intervention/s. The use of anesthetics is arising concern regarding its effects over the developing brain [26], and EA patients are exposed to more than one reintervention, especially during the first year of life, due to frequent postsurgery complications. Long-gap EA patients are the most affected in their neurodevelopmental status. Kubota et al. reported that mental retardation was recognized in 20% of their EA children, and pointed out that this condition was much higher than in the general population. Gischler et al. [18] also speculated that the most numerous interventions in EA patients are an important issue to be taken into account; they found that the need of medical appliances at home seemed to impede outcome and this effect was most prominent for tracheostomy, supplemental oxygen and nasogastric tubes. Our results in this area should arise concern about later outcomes (adolescence and adulthood) when other sequelae will appear such as poor performance at work, professional and academic disadvantages, emotional and behavior alterations, and poor self-image [21].

Regarding re-hospitalization for clinical causes, the most important cause for re-admittance is Low Respiratory Tract Infection (LRTI). Some children are re-admitted twice or more times during the first year of life. There are suggestions for preventive immunization against respiratory viruses, including RSV with palivizumab, because of the high burden of respiratory morbidity in these children. Our results are similar to those reported by Delacourt et al. [23], and Gischler et al. [18].

Surgical reintervention is a common problem in these children because of postoperative sequelae, associated malformations and sequential surgery repairs (colostomy, tracheostomy, gastrostomy) [10, 14, 27]. The percentage of the types of defect are very similar to those previously reported in the pediatric surgery literature. The surgical complications include anastomotic leaks, anastomotic stricture, recurrent tracheoesophageal fistula, tracheomalacia, altered peristalsis, GER and vocal cords dysfunction. With respect to the most common anastomotic stricture, the principal cause of surgical reintervention, we have a percentage equal to 47% at age 1 versus reported incidence up to 60% [28, 29].

Due to the complex issues that these babies have, we cannot stress enough the importance of nursing education for family, including ostomy care, gastrostomy feeding and appropriate use of medications, among others.

We consider it is remarkable the high level of concurrent complications these children suffer, so it is a must to assess them in a complete inter- and trans-disciplinary scope, to achieve better results, to avoid duplication of interventions, providing an integrated attention. Pediatric hospitals are in a privileged position to provide this kind of service taking advantage of the presence of all the pediatric subspecialties without increasing health resources costs [30, 31]. To our knowledge, there are no other larger reports of EA patients, assessed for such a long period on a complete interdisciplinary basis in a single center. Although it could be considered a relatively small sample size, because of the low prevalence of this malformation, we cannot expect a larger sample population. Another strength of our study is the high adherence to our protocolized surveillance.

One limitation of our study is that we did not analyze socioeconomic factors which represent a risk factor for suboptimal outcomes as previously reported [18].

Conclusions

The results of our comprehensive inter-disciplinary follow-up program show that patients with EA are at risk for long-term morbidity; in adulthood, other disabling morbidities may await these children. Further larger studies are advisable, employing this interdisciplinary, comprehensive scope, to confirm these data. The results of the matched-pairs analysis show that there are significant probabilities of worsening NPDI scores, so there is a compulsory need for an interdisciplinary, long-term surveillance. We strongly recommend interdisciplinary follow-up for them.

Declaration of interest

The Authors have no conflicts of interest to declare.

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