Journal of Pediatric Surgery (2013) **48**, 1664–1669

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Journal of Pediatric Surgery

www.elsevier.com/locate/jpedsurg

Esophageal atresia: Data from a national cohort

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http://dx.doi.org/10.1016/j.jpedsurg.2013.03.075

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Received 2 September 2012; revised 7 March 2013; accepted 9 March 2013

Key words:
Esophageal atresia;
Rare disease;
Epidemiology;
Prenatal diagnosis;
Neonatal surgery;
Cohort study;
Population-based registry

Abstract

Purpose: A prospective national register was established in 2008 to record all new cases of live-birth newborns with esophageal atresia (EA). This epidemiological survey was recommended as part of a national rare diseases plan.

Methods: All 38 national centers treating EA participated by completing for each patient at first discharge a questionnaire validated by a national committee of experts. Data were centralized by the national reference center for esophageal anomalies. Quantitative and qualitative analyses were performed, with *P*-values of less than 0.05 considered statistically significant. Results of the 2008–2009 data collection are presented in this report.

Results: Three hundred seven new living cases of EA were recorded between January 1, 2008, and December 31, 2009. The male/female sex ratio was 1.3, and the live-birth prevalence of EA was 1.8 per 10,000 births. Major characteristics were comparable to those reported in the literature. Survival was 95%, and no correlation with caseload was noted.

Conclusions: Epidemiologic surveys of congenital anomalies such as EA, which is a rare disease, provide valuable data for public health authorities and fulfill one important mission of reference centers. When compared with previous epidemiological data, this national population-based registry suggests that the incidence of EA remains stable.

Esophageal atresia (EA) with or without tracheoesophageal fistula (TEF) is a rare congenital malformation (MIM 189960) that occurs in 2.8 to 4.0 per 10,000 births [1,2]. The causes of EA remain largely unknown, although effects of environmental and genetic factors have been documented [3]. Progress in prenatal diagnosis may change the incidence in some countries, and environmental factors have been suggested to influence the occurrence of EA. Therefore, the prevalence of this congenital abnormality could change, even though data from various registries suggest that it remains stable over time. The live-birth prevalence is a good indicator for public health authorities, providing better recognition of such a rare disease. The prognosis for EA has benefited from advances in medical care including neonatal and surgical procedures. For all these reasons, population-based registries are necessary to assess changes in EA prevalence and outcome.

In this study, we report data collected prospectively from a national registry over a 2-year period.

1. Methods

1.1. Study population

A network of all the centers in France that treat EA was created in 2006 within the framework of the French national plan for rare diseases, and is coordinated by the National Reference Center for EA located in Lille University Hospital. A population-based registry of EA was created and began to collect all new cases of EA born in France from January 1, 2008. Based on previous information available on EA epidemiology and neonatal characteristics, a specific

questionnaire was created and underwent a number of rounds of development and testing. It was validated by a multidisciplinary national committee of experts, including epidemiologists, neonatologists, surgeons, and pediatricians. The questionnaire was first tested during a 6-month period in each center and was then reviewed and modified in a face-to-face meeting to establish the definitive version. The questionnaire was completed by the participating centers on a voluntary basis and a clinical research assistant helped with collecting the information when necessary. A physician and a research assistant checked each questionnaire and double-checked the data entered into the database, with careful attention being paid to avoid duplication of cases. When inconsistencies or a lack of information was found, the corresponding center was contacted to resolve the issue. Data included geographic origin, prenatal information, neonatal characteristics of the patient, associated anomalies, and surgical and early postsurgical outcome until first discharge from the hospital. EA was classified according to Ladd's classification [4]. Based on the estimated incidence of EA and on the national birth rate in France, we calculated the expected number of new cases to be between 150 and 250 per year. Exhaustiveness of inclusion was achieved by the voluntary participation of all the neonatal surgery teams and neonatal intensive care units within the national health system organization (tertiary health care centers). The inclusion criteria were all new living newborns with EA in France and its overseas territories. The sources of information were checked by three methods to enhance exhaustiveness. First, we checked with all centers via phone calls or emails that the team was enrolling all new patients; second, an audit was performed in 12 centers where our research assistant checked the source files; third, we crosschecked all questionnaires received against data obtained from the hospital information system database of each participating center. Patients included in this study were born between January 1, 2008 and December 31, 2009.

1.2. Statistical methods

Quantitative data were expressed as the median and range or as the mean and standard deviation (SD) according to their distribution. Normality of the distribution was assessed with the Shapiro–Wilk test. Qualitative variables were expressed as percentages. To compare the characteristics of children with type I and type III EA, a Chi-square test or Fisher's exact test was performed on qualitative variables and Student's *t*-test or the Mann–Whitney *U*-test on quantitative parameters. *P*-values less than 0.05 were considered statistically significant. Statistical analyses were performed using SAS software (SAS Institute, Cary, NC 25513; version 9.2).

2. Results

2.1. Prevalence of EA and characteristics of the population

Three hundred seven new live births with EA were recorded between January 1, 2008 and December 31, 2009. The calculated live-birth prevalence of EA was 1.8 per 10,000. The sex ratio (M/F) was 1.3.

Two hundred sixty-four children had distal TEF (type III) and four patients had a type IV condition (Table 1). In total, 87% of cases had the lower fistula type of EA. Thirty-one children had pure or type I EA (11%). Although polyhydramnios was present in 53.5% of cases, EA was suspected prenatally in only 20% of cases and justified prenatal transfer to a tertiary center in 17% of cases. Thirty-five percent of the children were born prematurely, and the mean birth weight of this population was 2561 ± 704 g. The median age of the mother at delivery was 30 years (range, 18–46 years). A family history of EA was found in six cases (2.5%). Fifty-three percent of the EA patients presented with at least one associated anomaly, with association with VACTERL in 23% of cases. Congenital heart disease (CHD) and great vessel anomalies were the most frequent anomalies, occurring in approximately one-third of the patients. Central nervous system and other non-VACTERL anomalies were present in 21 patients (duodenal atresia, labiopalatine cleft, central nervous system anomalies, and CHARGE syndrome). Associated congenital esophageal stenosis was found in three cases. Anorectal malformations were present

Table 1 Characteristics of the population according to the anatomical type of EA.

	All EA (n = 307)	Type I (n = 31)	Type III and IV (n = 268)	P (type I versus III and IV)
Polyhydramnios (%)	54	87	50	0.0007
Prenatal EA suspicion (%)	20	86	12	<0.0001
Prenatal orientation (%)	17	59	12	<0.0001
Diagnosis within the first day of life (%)	94	100	93	0.24
Gestational age (w) median (range)	38 (27–43)	36 (30–39)	38 (28–43)	<0.0001
Birth weight (g) mean (SD)	2561 (704)	2158 (560)	2611 (703)	0.0006
Associated anomalies (%)	53	58	52	0.56
Sex ratio (M/F)	1.3	1.3	1.3	0.9
Survival (%)	95	84	96	0.017

in 10% of patients. Diagnosis was established on the first day of life in 93.5% of cases, and surgery was performed before the 48th hour in 83% of cases. Surgical or endoscopic gastrostomy was necessary in 65 patients (22%). Fifty patients underwent delayed anastomosis with gastrostomy at birth, including 19 cases of pure EA, 11 long defects in type III patients, and three patients with upper pouch fistula (type II). For the 32 remaining cases, nine had pure EA and underwent primary anastomosis and systematic gastrostomy at birth, and 21 children with type III EA (17 premature) underwent gastrostomy with the decision for surgery being made case-by-case by the local team. The median artificial ventilation duration was 3 days (range, 0–117 days). The median length of first hospital stay was 22 days (range, 2–393 days) for the whole series. At the time of first discharge, 87% of patients were on full oral feeding. Gastroesophageal reflux treatment was given in 89% of cases and a Nissen procedure was performed in 7% of patients (10 patients, 70% type I EA) during the first year of life. The rate of preoperative tracheoscopy was low (21.5%). Twenty-two percent of patients required gastrostomy. Although primary anastomosis was achieved for 88% of neonates with EA, 1.5% (mainly those with pure EA) required lengthening techniques and 11.7% required delayed anastomosis. During the study period, gastric transposition was the preferred procedure when esophageal replacement was required (4%) (Table 2).

2.2. Survival

Sixteen deaths occurred during the first year of life (5%). There was no significant relationship between the caseload per center and mortality (Fig. 1). In the group with lower fistula EA type, premature births ($P < 0.001$), low birth weight ($P < 0.0001$), and associated anomalies ($P < 0.01$) were strongly associated with mortality. When cardiac abnormalities were studied alone, there was no correlation with mortality ($P = 0.7$). The survival rate was significantly better in type III atresia than in type I ($P = 0.01$) (Table 1).

Table 2 Medical treatments and surgical procedures performed in 307 cases of EA.

Standard primary anastomosis	88%
Difficult anastomosis	14%
Lengthening technique	1.5%
Delayed anastomosis	12%
Preoperative tracheoscopy	22%
Colonic transposition	0.5%
Gastric transposition	3.5%
Gastrostomy	22%
Aortopexy	1%
Proton inhibitor treatment at time of discharge %	86%
Prokinetic treatment at time of discharge %	68%

2.3. Type I EA

In type I EA, a higher rate of polyhydramnios, prenatal diagnosis, and prenatal transfer was observed compared with type III EA. The rate of low birth weight and premature birth was also higher. Associated anomalies and survival rate were similar in the two groups (Table 1). Fourteen patients (45%) underwent delayed anastomosis with native esophagus.

2.4. Caseload

Centers operating on fewer than five cases over the 2-year period had 3% mortality, centers operating on 5–10 cases had 5% mortality, and those operating on more than 10 cases had 5% mortality ($P = 0.7$). There was also no difference when centers performing 10 or fewer operations were compared with centers doing at least 10 ($P = 0.8$). Analysis of recurrent fistula, stenosis, and esophageal replacement rates did not show any influence of caseload: recurrent fistula occurred in 3% of patients in centers operating on fewer than five cases, 6% in centers operating on 5–10 cases, and 2% in those operating on more than 10 ($P = 0.26$); stenosis in 15%, 13%, and 24% respectively ($P = 0.10$); and replacement in 0%, 0%, and 2% respectively ($P = 0.47$).

3. Discussion

EA prevalence has remained stable over recent decades according to surveys of international registries such as EUROCAT [5,6], which currently includes 20 European countries and performs the surveillance of around 1.7 million births annually [7]. The French live-birth prevalence calculated for 2 consecutive years shows results (1.8/10,000) similar to those reported in different continents over more than 20 years [1,2,5,8].

EA prenatal diagnosis is now more commonly reported even if it is still rare in cases of isolated EA and lacks both sensitivity and specificity [9]. In this study, the rate of prenatal diagnosis of pure EA was much higher than that of types of EA with tracheoesophageal fistula, as polyhydramnios is frequent. The consequences of EA prenatal diagnosis could influence the live-birth prevalence in some countries depending on the legislation and practices for termination of pregnancy (ToP). French bioethics law for prenatal care and management allows ToP up to the time of birth, but is restricted to “nontreatable” malformations. Consequently, and considering the low rate of prenatal suspicion of EA in our country, ToP probably has a small effect on the currently detectable total prevalence, but improving the ability for early diagnosis might increase this.

The 307 new cases included in this register give a precise picture for public health authorities of EA presentation and care in the neonatal period, to aid improvement of care for these patients and their families, according to French rare

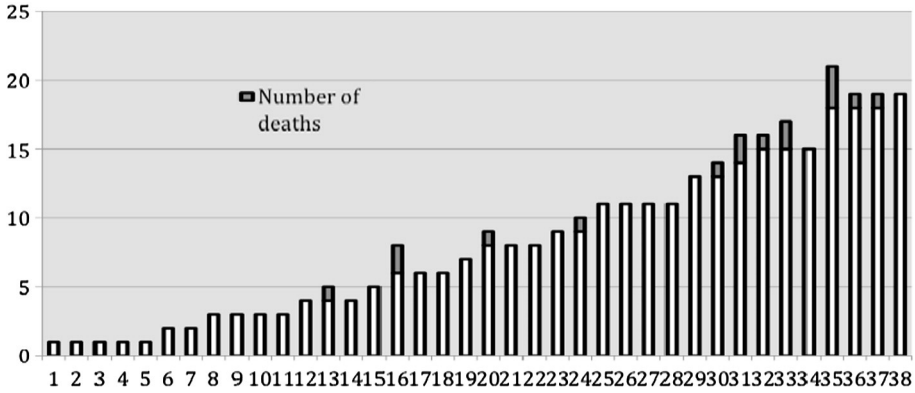

Fig. 1 Number of cases in 2008–2009 per center and survival. Each bar represents total cases during the 2-year study in each single center participating in the register. In white the number of alive patients, in black the dead patients.

diseases plans as the European plan (EUROPLAN). Isolated EA has been reported to have a better prognosis than nonisolated EA [9], which accounts for almost half of the population of EA patients. Our study also describes the overall pattern of management strategies used for neonates with EA in France. These data should be viewed with caution because of the small numbers and limited study time frame.

Caseload experience does not significantly affect the survival of patients with EA. Our study showed clearly that low levels of experience might be sufficient, as no difference in survival was noted in centers with fewer than five new cases per year. The question of the efficiency and quality of the follow-up of these patients remains. Long-term complications are well known in EA and long-term multidisciplinary follow-up seems to be beneficial [10,11].

Retrospective studies suggest that survival with EA in developed countries reached a plateau in the 1980s and seems to be currently stable at around 95% [12]. Major cardiac malformation and low birth weight (< 1500 g) are two predictors identified by Spitz using the modification of Waterston's risk-group classification [13], and are consistent with the present study. Although mortality analysis was statistically difficult in our series because of the low number of deaths occurring before 1 year of age, we observed that 14/16 neonates who died had associated malformations, with two cases of VACTERL syndrome. In addition, these children were all premature, which is a well-known cause of early mortality independent of associated malformations. Conversely, the prenatal diagnosis of associated anomalies, especially severe congenital heart malformations, can result in the termination of pregnancy and may explain why this mortality risk factor is currently less important than in the past [14]. Despite these limitations, our study based on a population-based registry suggests that survival of live-born neonates with EA is high (95%), and that the main determinants of death are type I EA, prematurity, and low birth weight.

Despite recent advances in surgical techniques for long gaps and in neonatal intensive care units, our results show clearly that type I EA continues to have a worse prognosis than type III and that morbidity is expected to be higher. Esophageal replacement techniques are numerous and cohort studies are still lacking. Only four gastric and one colonic replacement were performed before 1 year of age in our cohort, with an additional three lengthening procedures. The literature shows that pure EA has a worse functional prognosis than type III [15–17] and suggest the crucial role of multidisciplinary specialist clinics for long term follow up.

Tissue engineering techniques have both promise and challenges, and experimental models are numerous, but no human clinical experience with these has been reported [18,19].

EA epidemiological and outcome studies at a population-based national level are lacking. The present study shows the high effectiveness of a population-based registry based on a national network of neonatal pediatric surgery units. Our registry may provide an opportunity to give public health authorities invaluable information regarding the epidemiology and outcome of rare diseases such as EA. Results from such databases are also useful for any healthcare provider involved in prenatal and neonatal care to inform and best counsel the parents of an affected fetus or neonate.

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