National Esophageal Atresia Register

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Abstract

National Esophageal Atresia was created in 2008 by the National Reference Center for Esophageal Congenital Abnormalities created in 2006. Primary goal was estimation of live birth prevalence in France. A national network of surgeons and pediatricians was initiated and entire teams dealing with esophageal atresia accepted to participate in an exhaustive national register. A questionnaire was validated by a national committee and data were centralized in our center. Scientific exploitation showed that such database is useful for health authorities as for medical professionals. Live birth prevalence in France is at 1.9/10,000 births. Prenatal diagnosis is more common but its effect on prevalence is not yet fully understood. Associated congenital abnormalities are frequent and major malformations with termination of pregnancy can influence prevalence.

Keywords
- esophageal atresia
- register
- live birth prevalence

Introduction

Through application of the first Rare Disease Plan in France (2005–2010), 131 rare disease reference centers were labeled all over the national territory with a budget of 180 million euros for its second phase (2010–2014). Pediatric centers were around 30 out of the 131. Our team in Lille was designed in 2006 as the reference center for esophageal congenital malformations (Centre de Référence des Affections Congénitales et Malformatives de l'Oesophage [CRACMO]) since esophageal atresia (EA) and other rare congenital esophageal disorders (achalasia, congenital stenosis) are rare disease. Reference centers received set of specifications including the following: (1) to help and promote diagnosis of the disease; (2) to establish with the collaboration of health authorities national protocols for follow-up; (3) to coordinate research works all over the territory and participation to *epidemiological survey*; (4) to enhance and promote educational and disease information through the medical community; and (5) to participate in the organization of social network to help patients and their families. CRACMO is directed by a pediatric gastroenterologist with a team of surgeons, pediatric pulmonologists, ENT and neonatologist, psychologist, and speech therapist as well as adult gastroenterologist. On the other hand, CRACMO established a national network including all the 38 centers dealing with EA at birth distributed on the national territory (35) and overseas territories.[1] Questions about creating either a database for cohort long-term follow-up or an exhaustive register to have the most accurate picture of prevalence of EA over the national territory were discussed inside the reference center. The national register of all live born babies with EA was chosen and created in 2007 and first inclusion begun on January 1, 2008.

Arguments for initiating such register were as follows:

- EA is a rare disease, and as for many other rare diseases, real prevalence is based on historical series or textbooks. Many of these studies are from single center or included nonhomogeneous diseases population (fetal demise, pregnancy interruption, and different anatomical types). We wanted to have the exact prevalence of live birth EA in France since prenatal policies may have an impact.
- There were no specific register existing worldwide for EA.
- Actual data on early morbidity are lacking since prenatal diagnosis is more and more accurate with as a

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consequence fetal demises for severe associated abnormalities and recent progress in the neonatal care of these patients.

The European network of population-based registries for the epidemiologic surveillance of congenital anomalies, EUROCAT, gives prevalence of all congenital malformation observed over 1.7 million births from 43 registries in 23 countries. Prevalence founded, including fetal death and termination of pregnancy for fetal anomaly following prenatal diagnosis, was at 2.43/10,000 births.[2]

Register Objectives

- Primary: assess the live birth prevalence of EA in France
- Secondary:
  - Study of geographical distribution of EA in France and overseas territories
  - Assessment of survival rate and morbidity during the first year of life
  - Study of factors influencing survival and early morbidity
  - Study the influence of prenatal diagnosis on survival and early morbidity
  - Study digestive and respiratory status at 1 year of age

Methodology and Data Inclusion

Based on previous information available on EA epidemiology and neonatal characteristics, a specific questionnaire was created and underwent several rounds of development and testing. A multidisciplinary national committee of experts, including epidemiologist, neonatologists, surgeons, and pediatricians, validated it. The questionnaire was first tested during a 6-month period in each center and was then reviewed and modified in face-to-face meeting to establish final version which included two parts, one filled at the first discharge from the hospital and the second at 1 year of age. The questionnaire was completed by the participating centers on a voluntary basis and a clinical research assistant helped in collecting the information when necessary. A physician and a research assistant checked each questionnaire and double-checked the data entered into the database. Data included geographic origin, prenatal information, neonatal characteristics of the patient, associated anomalies, and surgical and early postsurgical outcome until the first discharge. EA was classified according to Ladd classification. The second part of the questionnaire was completed at 1 year of age. Teams participating were remembered for the second questionnaire if needed. When inconsistencies or a lack of information was found, the corresponding center was contacted to solve the issue. Questionnaire were centralized in our center, and from 2008 to 2011, we used Excel 2010 as software where data were filled. Since 2012, an electronic database (E-CRF) was created with the help of statistical and epidemiological department of our institution and online data inclusion was possible for the entire national network. 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.

Results

A total of 638 new cases were included from January 1, 2008, until December 31, 2011, and the live birth prevalence is at 1.9/10,000. There were 55 type I (8%) and 562 type III (88%). Survival at 1 year was at 94% (87% in type I and 93% in type III). Sex ratio (M/F) was 1.3. Associated abnormalities were found in 52%. Prenatal diagnosis was more frequent in type I (83%) than in type III (15%). During the first year of follow-up, the main causes of hospitalization were digestive in 52% of patients and respiratory in 48%. Although mortality was low, digestive and respiratory morbidities were frequent in the first year after EA repair and often required rehospitalization. This situation is associated with high health costs and has social and psychological effects on the relatives of these children. Information provided to the parents should be adapted to highlight these risks. EA follow-up is necessary, especially during the first year of life. High-risk groups of patients were identified. In a review in 2014 of 469 patients, we also confirmed that prenatal diagnosis was more frequent in type 1 and was associated with more in utero orientation, and the morbidity rate for infants who receive the diagnosis prenatally is significantly higher than for infants who receive the diagnosis postnatal, with no difference in mortality rate. A prenatal diagnosis allows the research of associated abnormalities that influence the morbidity. One other positive impact of a prenatal diagnosis is to give parents the choice to deliver close to a neonatal surgery unit to avoid postnatal transfer.

Pitfalls and Difficulties

We learned to manage many problems and difficulties since the creation of the register. We actually need a weekly meeting between the scientific responsible and the research assistant to have the latest idea about inclusion rate, delay in some centers, and missing data, and to organize visit of our assistant to some center, if needed, to help in questionnaire filling.

National qualification: The French National Institute for Health and Medical Research (INSERM) associated with French Institute for Public Health Surveillance (INVS) and the French National Cancer Institute (INCA) was charged to evaluate epidemiological registers in France since 2013 in the continuity of the National Register Committee who did our first evaluation in 2010 with qualification as a national register running from 2011 to 2013 with some recommendations. In 2015, a new evaluation renewed our qualification for 5 more years.

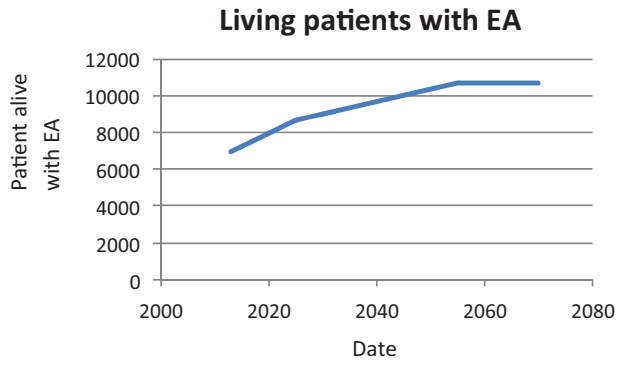

Fig. 1 Estimation of patients living in France with EA, based on measured prevalence and mortality rate.

Exhaustiveness: 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 in 2008 and in 15 centers in 2015 where our research assistant checked the source files and only one missing case was found (due to early death due to severe associated malformations in maternity wards before any surgery was scheduled); third, we cross-checked all questionnaires received against data obtained from the hospital information system database of each participating center.

Missing data: Missing data were numerous since the beginning, leading us to review the questionnaire 2 years after with excluding some data not very relevant or duplicated from the first questionnaire. Since 2010, missing data rate is stable. If important information is missing (i.e., survival, gender, etc.) during the filling procedure, we called directly each team when necessary and try to immediately obtain the exact information.

Delay in answering: Another difficult problem is the delay of some teams to fill the questionnaire at time. Continuous monitoring of this database allows us to find and alert each center. When serious difficulties are declared by our colleagues, our assistant schedules a trip and fills the questionnaires with the help of local team in each city he visits.

Statistical analysis: Data were included in Microsoft Excel 2010 software until December 31, 2012. With the help of our medical informatics department, an e-CRF was created giving the opportunity to each team to have direct coded access to fill data on a secured online questionnaire. Data are imported from the CRF to SAS software (SAS Institute, Cary, North Carolina, United States; version 9.2) for statistical analysis.

Benefits

Apart from epidemiological data useful for the health care policies in rare diseases at a national level, our register is also a source of scientific information about outcome of EA. Scientific exploitation was productive since the creation of our register. To allow a fair exploitation of these data, a chart was created to allow their use by any member of our network. Two reviewers from the scientific committee were designed to review any project using data from the register and rules of publication were a priori defined. A first descriptive paper of 307 patients was published after the first 2 years of registration and allow to assess the live birth prevalence at 1.9/10,000 live birth in France for the period 2008 to 2009.[3] Two other papers were published about morbidity at 1 year of age[1] and effect of prenatal diagnosis on outcome.[4] Several other studies are ongoing, that is, survival in EA in babies born under 1,500 g, or digestive, respiratory, and orthopedic status at 6 years of age. We are planning to develop a prospective cohort study from the patients included in the register.

Conclusion

A national register for one single congenital abnormality is a rare tool helping health authorities and support families groups. The calculated live birth prevalence associated with survival in EA allows us to extrapolate for the coming years that 8,000 patients with EA in the horizon of 2020 will be alive in France (►Fig. 1). Specific studies such as long gap EA, EA in premature newborn, and isolated versus associated abnormalities can profit from this population-based register and cohort or subgroups of patient can be studied. The national network of surgeons and pediatricians dealing with EA is the cornerstone of this register.

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