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Esophageal atresia at Daniel de Matos Maternity: a fifteen-year review

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Esophageal atresia at Daniel de Matos Maternity: a fifteen-year review

Atresia esofágica na Maternidade Daniel de Matos: uma revisão de quinze anos

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Abbreviation List

ARM – Anorectal Malformation

BW – Birth Weight

CHARGE syndrome – Coloboma, Hearth, Choanal Atresia, Retarded Growth, Genital Hypoplasia, Ear Deformities

CHUC – Centro Hospitalar e Universitário de Coimbra

DMM – Daniel de Matos Maternity

EA – Esophageal Atresia

ELBW – Extremely Low Birth Weight

FGR – Fetal Growth Restriction

GA – Gestational Age

GER – Gastroesophageal Reflux

GI – Gastrointestinal

IAC – Interatrial Communication

IVC – Interventricular Communication

NG – Nasogastric

NICU – Neonatal Intensive Care Unit

TEF – Tracheoesophageal Fistula

VACTERL association – Vertebral, Anal, Cardiac, Tracheal, Esophageal, Renal, Limb

Abstract

Esophageal atresia (EA) with/without tracheoesophageal fistula (TEF) is a rare congenital malformation, often associated with other congenital defects. Although diagnosis is mainly postnatal, its ultrasound prenatal suspicion has improved. These newborns need monitoring in Neonatal Intensive Care Unit (NICU), until they undergo surgery. Despite mortality being reduced closely to zero, morbidity is still a problem.

This study objective was to retrospectively characterize, by using descriptive and inferential statistics, the prenatal, delivery and postnatal data of EA newborns at Daniel de Matos Maternity (DMM), Centro Hospitalar e Universitário de Coimbra (CHUC).

A retrospective study from anonymized data of 18 newborns with EA, born between January 2007 and December 2021, admitted to the NICU of the DMM was performed. Prenatal, delivery and postnatal data were collected using medical records of these neonates, compiled with Microsoft Excel and analyzed by IBM SPSS statistics.

Out of the 18 newborns, 55.6% were females. The mean mother's age was 30.6 years. Prenatal suspicion was present in 33.3% of the cases, 100% in EA type A. The mean birth weight (BW) was 2276.4 grams and the mean gestational age (GA) was 35.7 weeks. 66.7% had other congenital anomalies: cardiac - 9 cases; other - 6 cases. All newborns underwent esophageal anastomosis. EA type C presented in 83.3% of the cases. 27.8% EA were long-gap. There was 100% survival rate. 88.9% developed at least one comorbidity.

In this study, there was no sex prevalence and no preponderance in advanced mother's age. Ultrasound prenatal suspicion was based on polyhydramnios and the non-visualization of the stomach, where EA type A had higher reports. Higher incidence of EA was found in premature newborns, thus also in newborns with low BW. Spontaneous breathing was preferred. Chest X-ray with an nasogastric (NG) tube was always performed, as well as an echocardiogram to exclude hearth malformations. A prevalence of EA type C and short-gap was found. Esophageal continuity was restored with anastomosis. The most frequent comorbidities were gastroesophageal reflux (GER) and esophageal stenosis.

This was the first study to analyze EA cases in DMM – CHUC. Improvement in prenatal surveillance could reduce morbimortality and improve management of these neonates. Postnatal meticulous evaluation of these newborns to classify EA and exclude other problems is imperative. Since mortality has been reduced, new studies should target morbidity and quality of life.

Keywords: Esophageal Atresia, Tracheoesophageal Fistula, Congenital Malformation, Prenatal Diagnosis, Polyhydramnios.

Resumo

Atresia esofágica (EA) com/sem fistula traqueoesofágica é uma malformação congénita rara, habitualmente associada a outros defeitos congénitos. Apesar do diagnóstico ser maioritariamente pós-natal, a suspeita ecográfica pré-natal tem melhorado. Estes recém-nascidos necessitam vigilância em Unidade de Cuidados Intensivos Neonatais (NICU) até à cirurgia. A mortalidade reduziu para aproximadamente zero, mas a morbilidade é ainda frequente.

O objetivo deste estudo foi caraterizar, usando estatística descritiva e inferencial, os dados pré-natais, nascimento e pós-natais de recém-nascidos com EA na Maternidade Daniel de Matos (DMM), do Centro Hospital e Universitário de Coimbra (CHUC).

Foi realizado um estudo retrospetivo, com dados anonimizados de 18 recém-nascidos com EA, entre janeiro 2007 e dezembro 2021, admitidos na NICU da DMM. Os dados pré-natais, nascimento e pós-natais foram colhidos de registos médicos destes recém-nascidos, compilados no Microsoft Excel e analisados pelo IBM SPSS statistics.

Dos 18 recém-nascidos, 55,6% eram do sexo feminino. A média da idade materna foi 30,6 anos. Suspeita pré-natal ocorreu em 33,3% dos casos, 100% na EA tipo A. A média da idade gestacional foi 35,7 semanas e do peso ao nascimento foi 2276,4 gramas. 66,7% apresentaram outras anomalias congénitas: cardíacas - 9 casos; outras - 6 casos. Todos os recém-nascidos foram submetidos a anastomose esofágica. A EA tipo C correspondeu a 83,3% dos casos. 27,8% das EA eram hiato-longo. A taxa de sobrevivência foi 100%. 88,9% desenvolveram pelo menos uma comorbilidade.

Neste estudo, não houve preferência entre sexos nem preponderância na idade materna avançada. A suspeita ecográfica pré-natal, onde a EA tipo A teve maiores taxas de deteção, foi baseada em: polihidrâmnios e não visualização do estômago. Maiores incidências de EA foram encontradas em recém-nascidos prematuros, consequentemente com baixo peso ao nascimento. A respiração espontânea foi preferida. A radiografia torácica com sonda nasogástrica e ecocardiograma para excluir malformações cardíacas foram realizados em todos. Uma prevalência de EA tipo C e hiato-curto foi encontrada. O estudo aponta uma alta frequência de complicações, especialmente refluxo gastroesofágico e estenose esofágica.

Este foi o primeiro estudo que analisou casos de EA na DMM – CHUC. Uma melhoria na suspeita pré-natal ajudaria a reduzir a morbimortalidade e a melhorar a gestão destes recém-nascidos. Uma avaliação meticulosa pós-natal para classificar a EA e excluir outros problemas

é imperativa. Visto que a mortalidade foi reduzindo, novos estudos deveriam considerar a morbilidade e a qualidade de vida.

Palavras-Chave: Atresia Esofágica, Fístula Traqueoesofágica, Malformações Congénitas, Diagnóstico Pré-natal, Polihidrâmnios.

Introduction

Congenital malformations affect around 3% of newborns, with a preponderance in the male sex. [1] Gastrointestinal (GI) malformations are the third most common, following orthopedic and central nervous system, with an incidence of 15%. The esophageal atresia (EA), anorectal malformation (ARM) and Hirschsprung's disease are the most prevalent GI malformations. [2]

EA is a congenital malformation in which the esophagus fails to develop, leading to an interruption in esophageal continuity. The esophagus ends blindly as a pouch, usually in the thorax, with or without a communication with the trachea, called tracheoesophageal fistula (TEF). [3] Despite being the most common GI malformation, it is a rare condition with an incidence of 1 in 3000/4500 live births worldwide. [4]

Even though the etiology of this pathology is not completely understood, it is believed that it is multifactorial. However, there is strong evidence of a genetic factor, probably polygenic. It is reported that the progeny of former EA patients has an increased risk. [5] Additionally, 6 to 10% of EA newborns have an association with chromosomal abnormalities, such as trisomy 13, 18 and 21 and some deletions (13q-, 17q- and 22q11-), being the trisomy 18 the most related to EA. [5,6] Moreover, three genomic regions, on chromosome 10q21, 16q24 and 17q12, were identified as being possibly correlated to the development of EA. On chromosome 10, located within intron 15 of the gene of the catenin alpha 3 (*CTNNA3*), the most significant variant related to EA was rs187017665. This gene encodes a protein part of the cadherin-catenin cell-cell adhesion complex and is a direct binding of beta-catenin (*CTNNB1*), that plays a role in embryonic proliferation and differentiation of the intestinal epithelium, which inactivation causes TEF in mice. On chromosome 16 the variant rs8046904 is the most associated with EA. It harbors the *FOX* gene cluster, that play an essential role in foregut development, which deletion can cause GI atresia. Lastly, on chromosome 17, the most associated variant with EA was rs3094503, located on the gene *HNF1B*, a gene required for the specification of the visceral endoderm, which duplications were found in syndromic EA/TEF. [5]

Furthermore, it is demonstrated that 50-70% of the EA patients have other associated congenital defects, the most common are cardiac (24%), genitourinary (21%), GI (21%), musculoskeletal (14%) and nervous system (7%). [7] When we have an association of three or more anomalies, the diagnosis of VACTERL (vertebral, anal, cardiac, tracheal, esophageal, renal, limb) is suggested, comprising approximately 10% of the EA patients. [8,9] Another possible anomaly association that could be present with EA is CHARGE (coloboma, hearth, choanal atresia, retarded growth, genital hypoplasia, ear deformities). [9]

The EA/TEF can be divided into five categories according to Gross classification (one of the most accepted classifications of EA), in relation with the presence and location of the TEF: Type A – isolated EA with no TEF (7-8% of all the EA); Type B – EA with proximal TEF (1-4%); Type C – EA with distal TEF (85%, being thus the most common); Type D – EA with proximal and distal TEF (3-4%); Type E also known as H-type – isolated TEF with no EA (3-4%). [8]

Usually, the diagnosis of EA is made after birth, in the first hours of life. It can be suspected through signs such as drooling, regurgitation, coughing, gagging and respiratory problems like apneic episodes and cyanosis, specially while or after being fed. [8] When these symptoms are present, a chest radiography taken with a nasogastric (NG) tube is mandatory. In this setting, a rolled-up tube in the proximal esophagus is expected and diagnostic of EA, whereas the presence of gas in the stomach and distal bowel occurs in the presence of TEF. [10] However, in some situations, a prenatal suspected diagnosis, based on ultrasound, is already present: polyhydramnios and the absence of gastric vesicle are the most used parameters, but they can be found in other pathologies and the latter is mostly present when there is no distal TEF, hence lacking specificity. More recently, other parameters like the detection of neck or chest sac from 32 weeks of gestation, known as the pouch sign, and the non-visualization of the lower thoracic esophagus are reported as reliable for the diagnosis of EA. Nevertheless, only one third of the EA cases are identified prenatally. [11] Following birth and diagnosis of EA, other exams, such as echocardiography, abdominal and lumbar ultrasound and bronchoscopy, should be performed in order to evaluate the possible association of others malformations and for anesthetic/surgical purposes. [12]

EA newborns demand monitoring in the Neonatal Intensive Care Unit (NICU): they need to be positioned with head elevation and require continuous saliva aspiration to prevent aspiration pneumonia; the use of broad-spectrum antibiotics, like ampicillin and gentamicin, is suggested but not mandatory. Furthermore, endotracheal intubation should be avoided to prevent iatrogenic gastric perforation. [13] The definitive treatment of this condition is the primary correction of EA/TEF, with an end-to-end anastomosis to reestablish the esophageal continuity. [9]

The prognosis is favorable, with 90-95% of patient survival, [8] being the majority of the deaths attributed to associated congenital anomalies, followed by sepsis. [14] Despite these survival rates, EA is associated with comorbidities, even after surgery, such as esophageal stenosis, dysphagia and gastroesophageal reflux (GER), with a reported incidence around 40%, 50% and 22-56% respectively. These may require medication, surgery or other treatment techniques, affecting the quality of life of these children. [15] EA survivors are at fourfold increased risk of Barrett esophagus, [16] which leads to a higher risk of adenocarcinoma and

epidermoid carcinoma, warranting dedicated surveillance through adulthood with routine endoscopies. [7,8]

The aim of this study was to retrospectively characterize the cases of EA at Daniel de Matos Maternity (DMM), Centro Hospitalar e Universitário de Coimbra (CHUC), in the last 15 years, from 2007 to 2021, by analyzing the Gross classification, risk factors, prenatal diagnosis, delivery, preoperative care, treatment, mortality and morbidity of EA neonates in this Tertiary Care Center.

Materials and Methods

After obtaining permission from the ethics committee of the CHUC, a retrospective descriptive study from anonymized data of 18 newborns with EA diagnosis, over 15 years, was performed. The inclusion criteria comprised of all the neonates born between January 2007 and December 2021, diagnosed with EA, that were admitted to the NICU of the DMM, which is a tertiary care referral center in Coimbra, Portugal. This was obtained searching the EA code on the unit's neonatal database of DMM and also using the clinical key coding list.

The demographic and clinical data were collected using electronic and paper-based medical records of neonates with EA hospitalized in the NICU. In the latter, the data of prenatal, diagnosis, delivery, NICU, surgery and comorbidities were accessed and compiled, guaranteeing all the anonymity necessary for this study.

Different instruments were used in this study. For the assessment of the prenatal data, obstetrics data related to the mother and fetus, information in the neonate clinical record was used. The postnatal and NICU care data relied on the Apgar score, chest radiography taken with an NG tube and regular monitoring analysis. To assess cardiac anomalies, an echocardiogram was performed. The EA type was classified using Gross classification.

Regarding prenatal data, the variables analyzed included mother's age, number of previous gestations, pregnancy surveillance, events during pregnancy, ultrasounds during pregnancy, suspected prenatal diagnosis of EA, the presence of polyhydramnios and other morphological anomalies in the ultrasound and fetal growth restriction (FGR) diagnosis. In relation to the delivery and the NICU data, the type of birth, the sex attributed at birth of the newborn, birth weight (BW), complete gestational age (GA), Apgar score, resuscitation, the chest radiography with the NG tube, ventilation, esophageal/oral continuous aspiration, antibiotics, complications, hours of life at transfer, echocardiogram and other congenital anomalies were recorded. In regard to surgery and comorbidities, the type of surgery performed, days of life at the surgery, type of EA, mortality and comorbidities (including GER and stenosis) were considered.

The data was stored in a Microsoft Excel table. IBM SPSS statistics software version 28.0 was used to execute a descriptive statistical analysis of the variables regarding prenatal antecedents, prenatal diagnosis, delivery, NICU care, surgery and comorbidities. The mean and the mode were used on the quantitative variables, while the variables classified as qualitative were converted into numerical ones and analyzed by using the frequency percentages and counts. A Fisher's Exact Test of independence was performed to examine the relation between polyhydramnios and FGR and the association between FGR and

hypoglycemia. A Mann-Whitney U test was employed to assess whether a difference exists between the complete GA at birth values of pregnancies previously with and without polyhydramnios. The previous test was likewise used to evaluate whether a difference exists between the complete GA at birth values of pregnancies previously with or without prenatal suspicion of EA. It was considered statistically significant when $p<0.05$.

Results

Between 2007 and 2021 the NICU of the DMM in Coimbra received 18 newborns with the diagnosis of EA. The yearly distribution of EA cases, years 2007-2021, varied from 0 to 3 cases per year (Figure 1).

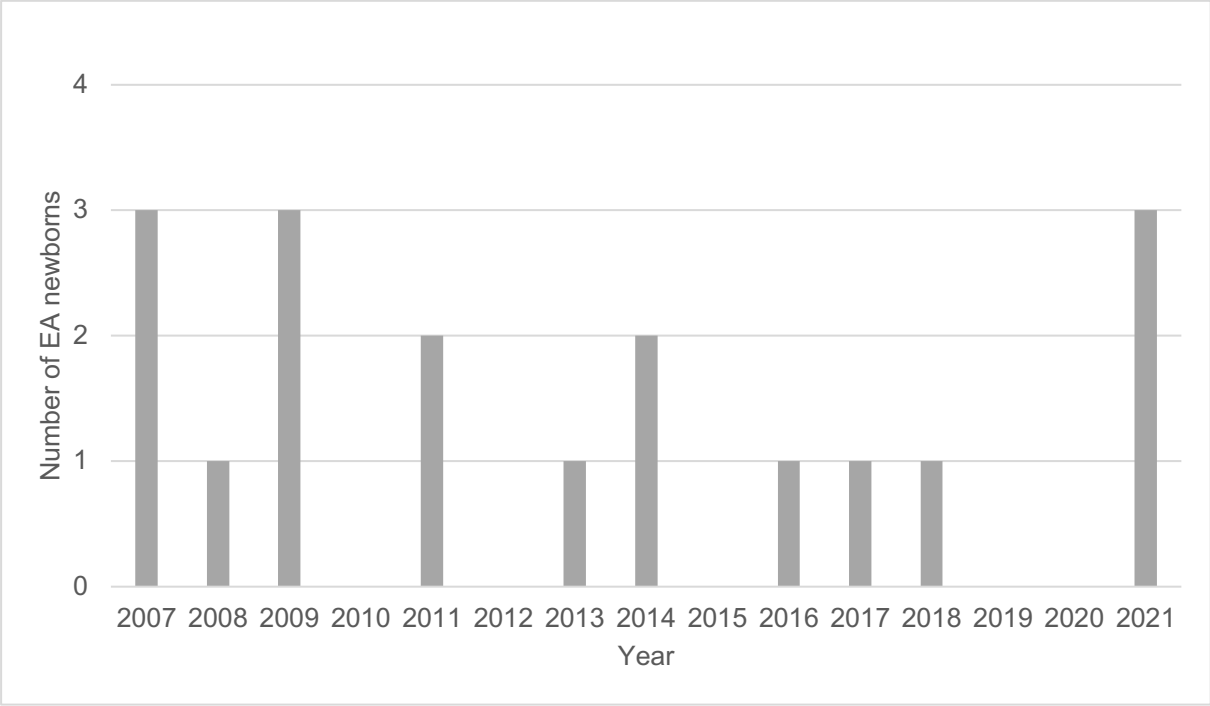

Figure 1. EA newborns distribution per year on DMM (n=18).

Out of the neonates with EA diagnosis, 55.6% (10 cases) were females and 44.4% (8 cases) were males. Regarding the mother's age, the mean was 30.6±5.9 years old, comprehending ages between 19 and 40 years. Concerning the obstetrics antecedents, the mean of previous pregnancies was 1.7±0.8, with the mode being 1 pregnancy (Table 1).

All of the pregnancies (18 cases) had complete and regular surveillance, distributed between private practice – 33.3% (6 cases), district hospital – 27.8% (5 cases) and central hospital - DMM – 38.9% (7 cases). The mean number of ultrasounds performed was 3.8±0.9 and the mode was 3 (Table 1). Of the 18 pregnant women, 10 (55.5%) had at least one event during pregnancy (Table 2). Group B Streptococcus colonization was noted in 4 of the pregnant women (22.2%).

Table 1. Demographic and prenatal data of newborns with EA diagnosis (n=18).

VARIABLES	ABSOLUTE NUMBER	FREQUENCY (%)	MEAN	STANDARD DEVIATION	MODE
SEX					
FEMALE	10	55.6			
MALE	8	44.4			
MOTHER'S AGE (YEARS)			30.6	±5.9	
NUMBER GESTATIONS			1.7	±0.8	1
PREGNANCY SURVEILANCE					
PRIVATE CLINIC	6	33.3			
DISTRICT HOSPITAL	5	27.8			
CENTRAL HOSPITAL	7	38.9			
NUMBER OF ULTRASOUNDS			3.8	±0.9	3

Table 2. Events reported during pregnancy (n=18).

VARIABLES	ABSOLUTE NUMBER	FREQUENCY (%)
FETUS EVENTS	5	27.8
AMNIOCENTESES	4	22.2
ABNORMAL CARDIOTOCOGRAPHY	2	11.1
MATERNAL EVENTS	2	11.1
GESTATIONAL DIABETES	1	5.6
PREECLAMPSIA	1	5.6
THREATENED PRETERM LABOR	2	11.1
OTHER EVENTS		
CONTRACTIONS/PELVIC PAIN	2	11.1
INDUCED LABOR	1	5.6
ERYSIPELAS INFECTION	1	5.6

In this study, suspected prenatal diagnosis of EA was present in 33.3% (6 cases), reported between 21 and 33 weeks of gestation, with a mean of 25.8±5.0 weeks, with an equal distribution between the 15 years. Polyhydramnios was present in 61.1% (11 cases) of all the pregnancies whereas other morphologic anomalies in the ultrasound were present in 33.3% (6 cases), being the non-visualization/reduction of the stomach the most common (66.7% of the other anomalies, present in 22.2% of the pregnancies – 4 cases, with concomitant polyhydramnios). When the prenatal diagnosis was suspected, polyhydramnios was always present (100%). Considering EA type A, 100% (2 cases) had prenatal suspicion of EA, having polyhydramnios and non-visualization of the stomach present. 44.4% (8 cases) of the cases had FGR. The relation between polyhydramnios and FGR was non-significant (p=0.630). From the 61.1% of the pregnancies not monitored in a central hospital (11 cases), 100% were transferred in-uterus to the DMM, out of these 63.6% (7 cases) had polyhydramnios and 18.2% (2 cases) had a suspicion of EA.

In regard to delivery, there was an equal distribution between cesarian (50.0% - 9 cases) and vaginal births (50.5% - 9 cases). The mean complete GA at birth was 35.7±3.1 weeks, with

GAs between 28 and 40 weeks, being the mode 37 weeks. The mean BW was 2276.4±727.6 grams (Table 3).

When adjusting for pregnancies with polyhydramnios (11 cases), 63.6% (7 cases) were cesarian births and 36.4% were vaginal births. The mean GA was 34.7±3.0 weeks, being the mode 35 and the mean BW was 2183.6±781.1 grams (Table 3). This study found statistically significant differences between the complete GA at birth in pregnancies with polyhydramnios (median 35 weeks) and pregnancies without polyhydramnios (median 37 weeks); U=16.0; p=0.038.

Once prenatal suspicion of EA was present (6 cases), the findings are cesarian births in 66.7% (4 cases) and vaginal births in 33.3% (2 cases), mean GA was 36.0±0.9 weeks, and the mean BW was 2297.5±391.3 grams (Table 3). This study did not find statistically significant differences between the complete GA at birth in pregnancies with prenatal EA suspicion (median 36 weeks) and pregnancies without it (median 37 weeks); U=32.0; p=0.704.

Table 3. Delivery data of all the pregnancies, the ones with polyhydramnios and the ones with prenatal suspicion of EA (n=18).

VARIABLES	ABSOLUTE NUMBER	FREQUENCY (%)	MEAN	STANDARD DEVIATION
ALL PREGNANCIES	18	100.0		
BW (GRAMS)			2276.4	±727.6
COMPLETE GA (WEEKS)			35.7	±3.1
TYPE OF DELIVERY				
CESARIAN	9	50.0		
VAGINAL	9	50.0		
PREGNANCIES WITH POLYHYDRAMNIOS	11	61.1		
BW (GRAMS)			2183.6	±781.1
COMPLETE GA (WEEKS)			34.7	±3.0
TYPE OF DELIVERY				
CESARIAN	7	63.6		
VAGINAL	4	36.4		
PREGNACIES WITH PRENATAL EA SUSPICION	6	33.3		
BW (GRAMS)			2297.5	±391.3
COMPLETE GA (WEEKS)			36.0	±0.9
TYPE OF DELIVERY				
CESARIAN	4	66.7		
VAGINAL	2	33.3		

The Apgar Score had a mean of 7.4±2.1 at the first minute, 9.0±1.3 at the fifth minute and 9.6±1.0 at the tenth minute, with the mode being 9, 10 and 10 respectively. Resuscitation was necessary in 27.8% of the cases (5 cases), using positive pressure ventilation in 3 cases (16.7%) and endotracheal tube in 2 cases (11.1%).

During the NICU stay, all newborns (18 cases) performed an X-ray with an NG tube and an echocardiogram. Ventilatory support was necessary in 16.7% of the neonates (3 cases): one that had extremely low birth weight (ELBW) and extreme prematurity (28 weeks), very low BW and prematurity (32 weeks) and the third case was a newborn with neonatal resuscitation, choanal atresia and retrognathism. Continuous aspiration was performed in 17 out of the 18 newborns (94.4%). Antibiotics were given in 44.4% of the cases (8 cases), mostly because of prenatal infectious risk. 33.3% (6 cases) reported complications in the NICU, being the most common hypoglycemia (4 cases). The relation between FGR and hypoglycemia was non-significant (p=0.618).

Congenital anomalies associated with EA were present in 66.7% (12 out of the 18 newborns). Cardiac anomalies were the most frequent with a frequency of 50.0% (9 cases), being the isolated interatrial communication (IAC) the most common (5 cases), followed by the association of IAC with interventricular communication (IVC) (3 cases) and isolated IVC (1 case). Besides cardiac anomalies, 33.3% (6 cases) revealed other congenital malformations: laryngeal clefts (2), ARM (1), minor dimorphisms (1), CHARGE syndrome (1) and suspicion of VACTERL association (1) (Table 4).

Table 4. Congenital malformations associated with EA, in the newborns with EA diagnosis (n=18).

VARIABLES	ABSOLUTE NUMBER	FREQUENCY (%)
ALL	12	66.7
CARDIAC	9	50.0
IAC	5	27.8
IAC + IVC	3	16.7
IVC	1	5.6
OTHER ANOMALIES	6	33.3
LARYNGEAL CLEFTS	2	11.1
ARM	1	5.6
MINOR DISMORPHISM	1	5.6
CHARGE SYNDROME	1	5.6
VACTERL ASSOCIATION	1	5.6

All these newborns were transported by a neonatal inter-hospital transport team to further evaluation by the Pediatric Surgery, with a mean of 11.1±10.1 hours of life at the transfer, with values between 1 to 40 hours. The latter were calculated with the exclusion of one case that had 96 hours of life at transfer because of extreme prematurity (28 weeks) and ELBW (770 grams).

In this study, according to Gross classification, type C was the most frequent with 83.3% (15 cases), followed by type A – 11.1% (2 cases) and type B – 5.6% (1 case), whereas types D

and E were not found. 27.8% of the EA were considered long-gap (5 cases), this corresponds to 100% of EA type A (2 cases) and to 20.0% of EA type C (3 cases out of 15) (Table 5).

Table 5. EA distribution in types according to Gross classification and between long-gap and short-gap (n=18).

VARIABLES	ABSOLUTE NUMBER	FREQUENCY (%)
EA TYPES		
TYPE A	2	11.1
TYPE B	1	5.6
TYPE C	15	83.3
SHORT-GAP EA	13	72.2
LONG-GAP EA	5	27.8

Regarding surgical intervention, all the newborns underwent anastomotic reconstruction of the esophageal continuity, with 17 neonates (94.4%) undergoing a primary reconstruction while one was submitted to a two-steps repair with Foker's method. Correction of the TEF was performed in all cases of EA types B and C (16 cases). Gastrostomy was necessary in 16.7% of the cases (3 cases). The mean of the days of life at the time of surgery was 2.5±0.9 days, with the mode being 2 days, these values were calculated with the exclusion of the first case where a delayed surgery was performed (7 months later).

When considering the morbidity and mortality, all newborns survived. The most frequent comorbidities and surgical comorbidities were: GER – 72.2% (13 cases), followed by esophageal stenosis with a prevalence of 55.6% (10 cases), dysphagia with 22.2% (4 cases) and esophagitis with 16.7% (3 cases).

Discussion

The present research represents the first descriptive study of the prenatal, delivery and postnatal data of newborns with the diagnosis of EA admitted in the NICU of the DMM in Coimbra, between 2007 and 2021.

In this work, there was a relatively equal distribution between females and males. This is in line with previous data that EA has no sex preference, [4,12] although some studies show that congenital malformations, including GI ones, have a male sex preponderance. [1,2,7]

Despite being reported that advanced maternal age (more than 35 years old) has a relation with EA development, [2,7] in this study the mean maternal age was below 35 years, with only four cases presenting advanced maternal age out of the 18 analyzed. It was also observed that most of the EA cases occurred on the first or second pregnancy, which is in concordance with previous studies that report that low birth number is a risk factor for the development of EA. [7] It was also verified that more than half of the pregnant women had at least one event during pregnancy. It was reported in other investigations that gestational diabetes, some maternal infections and exposure to some medications could be correlated to presence of EA in newborns. [2,7] The association of EA with the previously mentioned risk factors was not analyzed in this work due to lack of a control group.

The number of ultrasounds performed was relatively similar to those of normal pregnancies, with the majority of the cases having only three. In this study, all the gestations were monitored with an equal distribution between private clinic, district hospital and central hospital/DMM. However, all the pregnancies, that were not being monitored in a central hospital, were transferred to it still in uterus, mostly due to the presence of polyhydramnios and/or suspicion of EA. This is in agreement with recommendations that when there is a prenatal suspicion of EA, the parents are advised for the birth to occur in a tertiary referral center hospital, where an NICU and a Pediatric Surgical Unit are present, preventing further delays in management. [13] Nonetheless, these results made it impossible to compare the outcomes of these neonates between the pregnancies transferred still in uterus with the ones transferred postnatally.

Similar to previous reports, prenatal suspicion of EA based on antenatal ultrasound was present in one third of the cases with yearly equal distribution in the 15 years, [11,13] which occurred between the twenty-first and thirty-third week of gestation. This is in line with the literature stating that the diagnosis occurs in the second and third trimester, after the eighteenth week. [6,7] The prenatal suspicion of EA is based on the presence of polyhydramnios and the non-visualization of the stomach at the ultrasound. [7–11,13] Polyhydramnios was present in

around 60% of the pregnancies, similarly to previous data, whereas the non-visualization/reduction of the stomach was less frequent than in previous reports. [8] When prenatal diagnosis was suspected, polyhydramnios was always present and the non-visualization of the stomach was only in half of the cases. All the EA type A had prenatal suspicion of EA, with polyhydramnios and non-visualization of the stomach. This is in accordance with other authors who found that EA with no TEF had higher report rates of prenatal diagnoses that the other EA types. [8,13,15] FGR was present in almost 50% of the cases but it was not related to the presence of polyhydramnios. In this study, there were no cases of detection of neck or chest sac (pouch sign), nor the non-visualization of the lower thoracic esophagus, in contrast with existing evidence. [8,9,11,13]

When comparing the type of birth in the pregnancies with polyhydramnios and the ones with prenatal suspicion of EA, the cesarian birth was the most common in both, followed by vaginal birth, whereas when considering all the pregnancies there was an equal distribution between cesarian and vaginal birth. Although there was a prevalence of cesarian birth in pregnancies with prenatal suspicion of EA, this was also the case when considering the pregnancies with polyhydramnios. This is in line with previous data that prenatal diagnosis of EA is not a criterion for a cesarian birth, however this type of delivery should be performed when other anomalies and problems are anticipated and not for EA itself. [13]

The mean complete GA at birth, of the 18 newborns studied, was below 37 weeks. This was also the case when considering pregnancies with polyhydramnios or prenatal suspicion of EA. This is in agreement with previous data reporting a higher incidence of EA in premature newborns (bellow 37 weeks of gestation) rather than term ones, despite some studies concluding the opposite. [4,7] In correlation, it was also observed that the mean BW was below the 2500 grams, whether we considered all the pregnancies or just the ones with polyhydramnios or prenatal suspicion of EA, however with lower values when considering pregnancies with polyhydramnios. This is supported by other studies which revealed an association of EA with low BW. [7,12] Furthermore, it was found a statistically significant difference between the GA of pregnancies with polyhydramnios, with lower GA, comparing to the ones without polyhydramnios. The latter is in agreement with previous studies that state that polyhydramnios, implying a larger volume of amniotic fluid, is associated with an increased risk of preterm labor. [17]

The Apgar Score had only lower reports at the first minute, with a mean lower than 8, despite the mode being 9. At the fifth and tenth minute the values were between 9-10. Resuscitation was only necessary in a small number of cases, being in association with the Apgar score (in all cases the Apgar Score at the first minute was 7 or lower), and not with the EA itself.

As it was demonstrated in other investigations, all the newborns had a chest X-ray with an NG tube to verify the diagnosis of EA, which was confirmed when the NG tube was shown rolled-up in the proximal pouch of the esophagus. [9,10,12,13] Continuous aspiration was performed in practically all the newborns, as it is recommended by previous studies to prevent the risk of aspiration pneumonia. [8,9,12,13] The only case where it was not overtly stated, was probably due to omission in the medical records, since the newborn did not have contraindications to its use.

Spontaneous breathing is recommended in EA neonates. [8,9,13] In this study ventilation was needed in a low percentage of neonates: two cases for prematurity and one case for polymalformative syndrome, which was later confirmed as CHARGE. This is in agreement with other works, referring that ventilation should be avoided mostly because of the risk of iatrogenic gastric perforation when TEF is present. [8,9,13] Regarding antibiotics, they were used in almost half of the cases, but not only for the presence of EA but also in the context of prenatal infectious risk, such as extreme prematurity, premature rupture of membranes and fetal distress. There is not a consensus in whether prophylaxis with antibiotics should always be used in EA newborns nor which type of antibiotic should be administered, as shown in previous evidence. [9,13] A third of the neonates reported complications in the NICU, being the most common hypoglycemia. Although this complication could be associated with FGR, there was no association between them, demonstrated in this study. [18]

It is generally accepted that more than 50% of the EA newborns have at least one congenital malformation associated, [5,7,8,9,15] which is in line with this study. Cardiac anomalies are described as the most commonly associated with EA, with incidences varying in different studies, with values ranging from 23% to 86%. In this study, cardiac anomalies were present in half of the cases, being in accordance with the literature. [3,4,7,9,13,14] Among the cardiac anomalies, the IAC was the most common in this study, followed by IVC, as in previous works. [3,7] In all the cases an echocardiogram was performed for the exclusion of congenital hearth malformations. [8,13] Other congenital anomalies were present in one third of cases, in accordance to other studies [3]: two cases of laryngeal clefts and one ARM (VACTERL association was excluded), supporting previous reports, that state that both these pathologies have a higher incidence in EA patients than the general population. [8,9,12] Furthermore, it was found one case of CHARGE syndrome and one suspicion of VACTERL association. These two syndromes are strongly associated to the presence of EA, with the VACTERL association having a prevalence around the 10%. [3,4,8–10,15] These newborns were transferred to the pediatric hospital up until the 48 hours of life, with the majority being transferred in their first

day of life. The only exclusion was an extreme premature newborn with an associated ELBW, that needed a closed monitoring and stabilization before being transferred.

Regarding the EA type, similar to previous studies, type C was the most frequent, followed by type A. [1,3,10–12,15] There was one case of EA type B and types D and E were not found as they are less common. [7–9,13] Considering the distance between the two ends of the esophagus, EA can be divided in short-gap and long-gap. The latter is usually characterized by a gap longer than 2-3 cm or higher than 2 vertebral bodies and it is more common in EA type A and B. [4,9,19] In this study, a prevalence of short-gap EA was found, with only 30% of long-gap EA. This was somewhat in accordance to other studies that reported that long-gap EA had a prevalence of around 10-30%. [15,19] All the EA type A cases present in this report were confirmed as long-gap, compared to only 20% when considering EA type C.

Surgery was performed in the first days of life, mostly on the second day. This is in line with previous studies that report that the correction of EA should be performed in this period (first days of life), to reduce mortality. [3,6,8,20] All the newborns underwent anastomotic reconstruction of the esophageal continuity, as it is recommended. [7–9,12,19,20] In the majority of the neonates, similar to previous data, a primary reconstruction was performed, with only one case of a two-step repair of the esophageal continuity after Foker's method – which consists in using traction sutures to enable esophageal stretching, mostly executed in long-gap EA, when primary reconstruction is not possible. [4,9,19] The Foker's method was necessary in an EA type C, presented as long-gap, in which the primary reconstruction wasn't feasible. The correction of the TEF was performed in all the EA types whenever present. Gastrostomy was necessary in three newborns: in the two EA type A and in the long-gap EA type C that went through Foker's method. In previous studies, it was reported that gastrostomy was required in the majority of the cases where a long-gap was found, mostly in type A, or in the presence of a wide TEF with respiratory distress. [19,20]

There was no mortality reported in this study, as similar to prior records stating an increase in the survival rate, greater than 90% in most cases, with mortality mostly only occurring in those of extreme prematurity or other associated congenital anomalies. [8,9,12,14,15,20]

Comorbidities associated with EA are common, not only after birth, but also in the subsequent years of life. [7,8,16] These comorbidities had a prevalence around 90% in this study, with GER being the most frequent with reports up to 70%. Although other studies report lower incidences, between 40-60%, they still consider GER as a highly prevalent comorbidity in EA patients. [9,16] Esophageal stenosis was the second most common comorbidity associated with EA, with a frequency of circa 55%, slightly higher than previous data with reports of

approximately 40%. [9,15] Lastly, dysphagia and esophagitis were also present, with rates around 22% and 17% respectively. These had lower reports than previous works, nonetheless still somewhat prevalent. [8,15,16]

This study has several limitations such as: the small sample size (since EA is a relatively rare disease); it's retrospective nature, which restricted the collection of some data; for being a single-center work, which could create bias and reduce sample size, as the DMM is a tertiary care referral center; and the absence of a control group, which could have allowed some more conclusions. To overcome these limitations, a national registry or prospective multicenter study with a larger sample size could be planned.

Conclusion

In summary, this report was the first descriptive retrospective study performed with newborns diagnosed with EA admitted in the NICU of the DMM in Coimbra, between 2007 and 2021. The results revealed neither gender nor advanced maternal age prevalence, with the majority of the cases occurring in the first two pregnancies. Additionally, more than 50% of the pregnancies reported an event during pregnancy. One third of the cases had ultrasound suspected prenatal EA, between the twenty-first and the thirty-third weeks of gestation, mostly based on polyhydramnios and some on the non-visualization of the stomach. Moreover, all the EA type A cases had prenatal suspicion of EA. Also, FGR was present in half of the cases.

In this research, the most common type of birth performed was the cesarian birth in both pregnancies with polyhydramnios and pregnancies with prenatal suspicion of EA. It was also found that there was a preponderance of EA in preterm newborns and in newborns with low BW. Furthermore, an association between lower GA and the presence of polyhydramnios was found. Resuscitation was mostly necessary in cases of an Apgar score lower than 7 at the first minute. In all the cases, an X-ray with an NG tube was performed to confirm the EA diagnosis. In all cases (excluding the one omitted) continuous aspiration of saliva was performed, in contrast to ventilation that was only required in a small percentage of cases, whereas antibiotics were used in around half of the cases. In the NICU, one third developed complications, mostly hypoglycemia. It was found that more than half of the EA neonates had another congenital anomaly associated, mostly structural cardiopathy – IAC and IVC. Thus, all the newborns went through an echocardiogram to exclude cardiac anomalies. Other associated malformations, such as laryngeal clefts, ARMs, VACTERL and CHARGE were found in one third of the cases. All newborns, excluding one, were transferred to the Neonatal Surgical Reference Unit in the first 48 hours of life to undergo surgical correction of the EA/TEF.

Regarding EA types, in this report, type C was the most common. Long-gap EA was present in almost one third of the cases (all EA type A cases). Although there was a relatively significant prevalence of long-gap EA, the main surgery performed was still the primary anastomosis of the esophageal continuity, mostly in the second day of life, with only one case undergoing Foker's method. Gastrostomy was only necessary in three cases of long-gap EA. There was zero mortality reported in this study. However, significant morbidity was reported in these children, related to EA comorbidities such as GER, esophageal stenosis, dysphagia and esophagitis.

To conclude, EA remains a challenging pathology in newborns. An accurate prenatal suspicion of EA would be of extreme importance to reduce mortality and morbidity and to improve the

management of these neonates, with immediate monitoring in an NICU and brief time to surgery. Despite the advances in prenatal diagnosis, it was positive in only in one third of our cases. Efforts should be made to improve detection rates and eventually also consider novel markers. After birth, it is important to confirm the diagnosis, the type of EA present and check the existence of other malformations, since these can have a huge impact in the management of these neonates. With increasing numbers of neonates surviving EA, new studies should concern issues related to morbidity and quality of life of these children.

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