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ORIGINAL ARTICLE

Surgical correction of tracheo-oesophageal fistula and oesophageal atresia in infants with VACTERL association: a retrospective case–control study

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Abstract
Introduction VACTERL is a rare, non-random association comprising at least three major component features defined by the acronym, and including Vertebral anomalies, Anorectal malformations, Cardiac defects, Tracheo-oEsophageal fistula with or without oesophageal atresia (TOF/OA), Renal abnormalities and Limb anomalies. The aim of this study was to compare the post-operative outcomes following surgical correction of TOF/OA in infants with VACTERL and isolated TOF/OA.
Methods A retrospective case–control study comparing infants with VACTERL (case group) versus infants with isolated TOF/OA (control group) that underwent surgical correction of TOF/OA at our centre between January 2006 and December 2011. Patient demographics, types of anomalies, operative techniques and post-operative outcomes were collected using inpatient and outpatient records.
Results We identified 30 consecutive infants with TOF/OA. Five infants had VACTERL (17 %) and 15 infants had isolated TOF/OA (50 %). There was no significant difference in the gestational age ($P = 0.79$), birth weight ($P = 0.69$) or operative repair ($P = 0.14$) between groups. Overall, surgical correction of TOF/OA led to satisfactory morbidity. Infants with VACTERL were not at higher risk of post-operative complications, such as oesophageal stricture ($P = 0.17$) or gastro-oesophageal reflux ($P = 1.0$), compared to infants with isolated TOF/OA.
Conclusions VACTERL association does not increase the risk of post-operative complications following TOF/OA repair.

Keywords VACTERL association · Tracheo-oesophageal fistula · Oesophageal atresia

Introduction

VACTERL is a rare, non-random association of complex congenital abnormalities [1, 2]. It has an estimated prevalence of between 1 in 10,000 and 1 in 40,000 infants [3]. The phenotypic characteristics required for the diagnosis of VACTERL have been extensively debated since its original description, but most clinicians agree that at least three major component features (MCFs) are required. These include Vertebral anomalies, Anorectal malformations, Cardiac defects, Tracheo-oEsophageal fistula with or without oesophageal atresia (TOF/OA), Renal abnormalities and Limb anomalies. The aim of this study was to compare the post-operative outcomes following surgical correction of TOF/OA in infants with VACTERL and isolated TOF/OA.

Methods

Our study was approved by the ethical review board of the John Radcliffe Hospital, Oxford. The hospital database was searched to identify all infants with TOF/OA between January 2006 and December 2011. A diagnosis of VACTERL was made if an infant possessed at least three

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Table 1 Spectrum of major component features in infants with VACTERL

Gender	Gestation (weeks)	Birth weight (g)	Vertebral	ARM	Cardiac	TOF/OA	Renal	Limbs	Non-VACTERL
M	35	2,700	Hemivertebrae (L1), supernumerary rib (right)	Recto-urethral fistula	–	Long-gap OA with distal TOF	Renal agenesis (left)	–	–
F	36	2,080	Hemivertebrae (T3/T4), fusion of adjacent ribs (bilaterally)	–	Large AVSD, pulmonary stenosis	OA with proximal TOF	–	–	Cleft lip/palate
F	37	2,780	Hemivertebrae (T3), fusion of adjacent ribs (left), supernumerary rib (right)	–	Fallot-type DORV	Long-gap OA with distal TOF	Renal agenesis (left)	–	Hypoplastic left lung, pulmonary artery and vein
M	38	3,040	Hemivertebrae (T8), fusion of adjacent ribs (bilaterally)	–	Isolated ASD	OA with distal TOF	–	–	–
F	40	2,710	–	Recto-vestibular fistula	–	OA with proximal TOF	Renal agenesis (right)	Polydactyly	–

ASD atrial septal defect, *ARM* anorectal malformations, *AVSD* atrioventricular septal defect, *DORV* double outlet right ventricle, *TOF/OA* tracheo-oesophageal fistula/oesophageal atresia

MCFs, and had no clinical signs or chromosomal abnormalities consistent with overlapping syndromes. Congenital defects that are recognised features of prematurity, such as patent ductus arteriosus (PDA), patent foramen ovale and cryptorchidism, were not included as MCFs. Infants with hydrocephalus, i.e. VACTERL-H syndrome were also excluded.

Patient demographics, types of anomalies, operative techniques and post-operative outcomes were collected using inpatient and outpatient records. Categorical data are described by frequency and percentage, and continuous data are described as median (range) or mean ± SD. To determine significant differences between groups, a Fisher exact test was used for categorical variables and a Mann–Whitney *U* test was used for continuous variables. A P value ≤ 0.05 was considered as significant.

Results

Population

We identified 30 consecutive infants with TOF/OA between January 2006 and December 2011. Five infants had VACTERL (17 %) and 15 infants had isolated TOF/OA (50 %). The remaining infants had CHARGE syndrome ($n = 2$), Trisomy 18 ($n = 2$), Treacher-Collins syndrome ($n = 1$), Townes-Brocks syndrome ($n = 1$), or, other anomalies that were not consistent with an identifiable syndrome ($n = 4$). The spectrum of MCFs in infants with VACTERL is outlined in Table 1.

Perinatal morbidity in infants with VACTERL

Antenatal complications included polyhydramnios ($n = 5$), maternal insulin-dependent diabetes mellitus ($n = 1$), intrauterine growth retardation ($n = 1$) and twin reversed arterial perfusion syndrome ($n = 1$). There was no parental consanguinity [4].

There was no significant difference between the gestational age ($P = 0.79$) or birth weight ($P = 0.69$) in infants with VACTERL and isolated TOF/OA (see Table 2). Genetic analysis was performed on all infants with VACTERL and results were negative [5].

VACTERL including TOF/OA

Five infants (2 males) had VACTERL. Four infants were diagnosed antenatally when polyhydramnios and a small/absent fetal stomach bubble were evident on fetal ultrasound scans. Two infants had OA with proximal TOF (40 %) and three infants had OA with distal TOF (60 %). Two infants had long-gap OA (defined as a distance of four or more vertebral bodies whilst under tension [6]). Three infants underwent thoracotomy, fistula ligation and primary OA repair on day 1 of life. One infant with long-gap OA underwent thoracotomy, fistula ligation and gastrostomy. Delayed repair under anastomotic tension was performed

Table 2 Incidence of post-operative complication following surgical correction of TOF/OA in infants with VACTERL and isolated TOF/OA

	VACTERL ($n = 5$)	Isolated TOF/OA ($n = 15$)	P value
Gestational age (weeks)[a]	37.2 ± 1.9	37.1 ± 3.5	0.79
Birth weight (g)[a]	2,609 ± 783	2,662 ± 353	0.69
Cardiac anomaly	4	10	1.0
TOF with OA			
Proximal fistula	2	2	0.53
Distal fistula	3	10	1.0
Proximal and distal fistula	0	1	1.0
Isolated OA	0	2	1.0
Long-gap OA	2	2	0.53
Primary repair	3	14	0.14
Delayed repair	2	1	0.14
Post-operative morbidity			
Anastomotic leak	1	0	0.25
Tracheomalacia	2	1	0.14
Re-fistula	0	0	NA
Oesophageal stricture	4	6	0.17
Gastro-oesophageal reflux	2	5	1.0
Fundoplication	1	1	0.45*
Patient survival	4	14	0.45*

NA not applicable

[a] mean ± SD

* one-tailed Fisher exact test

8 weeks later. The second infant with long-gap OA had Fallot-type double outlet right ventricle (DORV), and left hypoplastic lung, pulmonary artery and pulmonary vein. On day 1 of life this infant underwent thoracotomy, fistula ligation and gastrostomy, but primary repair was considered inappropriate due to intra-operative respiratory distress. Cervical oesophagostomy was performed 11 weeks later, although the infant died from heart failure before oesophageal replacement surgery was performed.

Post-operative morbidity included oesophageal stricture ($n = 4$), gastro-oesophageal reflux (GOR; $n = 2$), tracheomalacia ($n = 2$) and anastomotic leak ($n = 1$). No infant developed fistula recurrence. A contrast study was used to diagnose oesophageal stricture in symptomatic infants. Four infants underwent 2–5 endoscopic balloon dilatations for stricture formation. Anti-reflux surgery was performed in one infant. In comparison to infants with isolated TOF/OA, infants with VACTERL were not at higher risk of post-operative complications (see Table 2).

A single infant (birth weight of 2,780 grams) with VACTERL died of heart failure secondary to pulmonary hypertension and complex congenital heart disease (Fallot-type DORV). They underwent total cardiac repair at 4 months of age, but died 2 months later. There was no difference between the overall survival of infants with VACTERL (80 %) and isolated TOF/OA (93 %) (see Table 2).

The median follow-up was 2 years (range 1–6 years).

Discussion

Early observational trials outlining the surgical management of TOF/OA in infants with VACTERL used a temporary gastrostomy prior to definitive repair [7–9]. Since then, corrective surgery of TOF/OA has developed to favour primary repair; often within 1–2 days of birth. In our study, all infants with short-gap OA underwent primary repair, and only those with long-gap OA or intra-operative complications required temporary gastrostomy.

Gastro-oesophageal reflux and oesophageal stricture are the most common post-operative complications associated with OA repair occurring in approximately 40 % and 30 % of cases, respectively [10]. Risk factors for oesophageal stricture include anastomotic leak, GOR and anastomotic tension [6, 10]. In our study, infants with VACTERL were not at statistically higher risk of anastomotic leak, GOR or oesophageal stricture. In addition, there was no difference in the incidence of long-gap OA requiring anastomotic tension. Our findings contrast those reported in a recent publication, in which VACTERL was identified as a significant risk factor (univariate analysis: $P = 0.013$) for oesophageal stricture following OA repair in a larger retrospective cohort ($n = 62$) [11].

Our study has two major limitations that should be considered when interpreting the findings. First, this is a retrospective study and prone to the disadvantages associated with such trial design. Second, our sample size is small and underpowered. Nevertheless, it is well recognised that the prevalence of VACTERL is extremely low; estimated between 1 in 10,000 and 1 in 40,000 infants [3]. Registry data also shows that TOF/OA is not a universally expressed phenotypic characteristic in these infants; occurring in around 50–80 % of cases [12–14]. Furthermore, unlike other studies [15, 16], we have only included infants with at least three MCFs of VACTERL and a negative genetic screen, as well as excluding MCFs that are consistent with prematurity (e.g. PDA). These factors mean that although the size of the study group is small, we are confident that these infants were appropriately diagnosed [5].

In summary, we have outlined the surgical management of TOF/OA in infants with VACTERL at our institution over a 6-year period. We can conclude that VACTERL is not associated with a higher risk of surgical morbidity or mortality compared to isolated TOF/OA.

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