# Oesophageal Atresia, Related Malformations, and Medical Problems: A Family Study

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Oesophageal atresia (OA) and tracheooesophageal fistula (TOF) are lifethreatening malformations of generally undefined cause. Previous reports of familial cases suggest a genetic contribution. The pattern of inheritance appears non-Mendelian, i.e., multifactorial. Individuals with OA/TOF often have other malformations and medical problems. The aim of this study was to determine the association in OA/TOF cases and healthy control subjects of associated malformations, midline defects, and medical conditions. We also investigate the relationships of these conditions in the relatives of the cases and controls. The results show that infants with OA/TOF frequently have VACTERL anomalies (vertebral, 17%; anal, 12%; cardiac, 20%; renal, 16%; limb, 10%) and other midline defects (cleft lip and palate, 2%; sacral dysgenesis, 2%; urogenital anomalies, 5%). The following medical problems were also reported: oesophageal dysmotility, 21%; gastrooesophageal reflux, 22%; chest infections, 6%; and autonomic dysfunction, 0.5%. The first-degree relatives of children with OA are much more likely to have one of the aforementioned malformations or medical conditions when compared with the control group: one or more VACTERL anomalies (P < 0.01), gastro-oesophageal reflux (P < 0.05), recurrent respiratory infections (P < 0.05), and autonomic dysfunction (P < 0.001). The more distant relatives also show an increased incidence of such problems al-

KEY WORDS: oesophageal atresia; tracheooesophageal fistula; VAC-TERL association; midline defects

## INTRODUCTION

Oesophageal atresia (OA) with or without tracheooesophageal fistula (TOF) affects 1 in 3,000 newborn infants. Cause and pathogenesis of these birth defects remain unknown; several familial cases have been reported [Engel et al., 1970; Dennis et al., 1973; Erichsen et al., 1981; Pletcher et al., 1991; McMullen et al., 1996]. In attempts to unravel the cause, a number of epidemiological studies have been carried out. These studies tried to elucidate the relative genetic and environmental contributions by analysing spatial and temporal clustering [Robert et al., 1988, 1993; Barbujani et al., 1989; Castilla et al., 1990; Depaepe et al., 1993; Yang et al., 1994; Rittler et al., 1997], socio-economic factors [David and O'Callaghan, 1975], and ethnic origins [Harris et al., 1995; Torfs et al., 1995; Leck and Lancashire, 1995]. Isolated OA, and OA associated with other anomalies or chromosomal disorders, have been compared to identify causal differences [Harris et al., 1995; Rittler et al., 1996].

This study takes a different approach, aiming to characterise the families of individuals with OA. The presence of associated malformations and related medical problems was determined by posing relevant questions to these families.

Oesophageal atresia is often associated with other malformations. VACTERL (vertebral, anal, cardiac, tracheo-oesophageal, renal, and limb anomalies) is the

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though in this case the data must be viewed with caution. The results confirm that the associated malformations and related medical problems occur significantly more frequently in the relatives of individuals with OA/TOF. These families may prove valuable for linkage analysis in an attempt to determine the genetics of OA/TOF. Am. J. Med. Genet. 85:31–37, 1999. © 1999 Wiley-Liss, Inc.

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most common association with 14-36% of individuals with OA/TOF having two or more VACTERL anomalies [Torfs et al., 1995; Rittler et al., 1996]. Other associations described include CHARGE, PHAVER, and SCHISIS associations and Goldenhar syndrome [Chittmittrapap et al., 1989; Powell et al., 1993; Sutphen et al., 1995; Tellier et al., 1998]. OA often occurs in the presence of a number of chromosomal anomalies, in particular trisomy 18 and 21 [Benady and Harris, 1969; Harris et al., 1995; Torfs et al., 1995; Beasley et al., 1997]. Children with OA frequently have additional medical problems following successful surgical repair of the primary malformation. Recurrent respiratory infections [Dudley and Phelan, 1976; Checuti and Phelan, 1993b], swallowing difficulties [Smith and Beck, 1985; Checuti and Phelan, 1993a] and intractable gastro-oesophageal reflux [Ashcraft et al., 1977; Parker et al., 1979; Jolley et al., 1980] are common causes of morbidity.

OA/ TOF may represent part of a spectrum of disorders resulting from the additive effects of genetic and possibly environmental factors. Mild phenotypes may be responsible for the related medical problems in the absence of an overt malformation (for example, swallowing difficulties in the presence of an intact oesophagus), or other less-severe malformations associated with OA such as mild cardiac, thumb, renal, and vertebral anomalies. The severe end of the spectrum would be the full VACTERL association with a large number of related medical problems. If this hypothesis is correct, then one would expect that the occurrence of such anomalies and related medical problems would be higher in the relatives of individuals with any VACTERL component.

The aim of this study is two-fold: Firstly, it investigates the association of other defects and related medical problems in OA cases and the control individuals, and secondly, it attempts to determine the occurrence of related malformations and medical problems in the first-degree and more distant relatives of individuals with any VACTERL component.

The process of data collection used in this study focuses on the whole family, in contrast to the medical notes and malformation registry entries used in previous studies, which deal primarily with data pertaining to the affected individual.

# MATERIALS AND METHODS

The data were collected in the form of a case-control postal questionnaire over the period spanning August 1997 and June 1998. The study families ("OA families") are all either members of TOFS, a charitable support group based in the United Kingdom, or KEKS, a sister organisation based in Germany. The OA family is defined as the family of a child with OA with or without TOF. Each family received an explanatory letter and a questionnaire. In total 1,700 families were contacted, and 579 responded (response rate 34%).

The control group comprises families with at least one child of a similar age and from the same geographical area as the OA case. The OA families were asked to select up to three additional families, which fulfilled

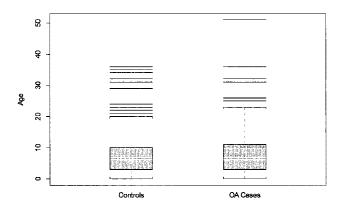


Fig. 1. Age range distribution of cases and control individuals.

those two criteria. Out of 4,962 control questionnaires sent out 1,031 were completed (response rate 21%). The average number of control individuals per OA family was 1.8

Information obtained from the questionnaires included:

- Details about the OA/control case: date of birth, birth weight, prematurity, current weight and height, all birth defects and medical problems.
- 2. Details about the first-degree relatives: date of birth, all birth defects and medical problems (including age of onset to exclude age-related rather than congenital medical problems).
- Perinatal factors related to the OA/control case and their sibs including exposure to environmental agents, drugs, etc.
- Obstetric history of the mother of the OA/control case.
- Information regarding the presence of birth defects and related medical problems in more distant relatives.

The questions ranged from very specific, such as those seeking information about particular medical problems, to open (for example, when enquiring about exposure to environmental factors or drugs during the first trimester of pregnancy).

The OA cases were subdivided into isolated cases (in which OA with or without TOF was the only anomaly), and complex cases (in which one other VACTERL association anomaly was reported). The data were entered into the statistical package SPSS version 8.0 for Windows. Significant associations in cross-tabulations were assessed using chi-squared tests or, where there were small numbers, using Fisher's exact test.

TABLE I. Association of Other VACTERL Malformations in OA and Control Groups

Malformation present	OA cases n (%)	Controls n (%)	<i>P</i> -value
Rib or vertebral anomaly	96 (17)	2 (0.2)	< 0.0005
Ano-rectal malformation	70 (12.1)	0 (0)	< 0.0005
Cardiac anomaly	115 (19.9)	7(0.7)	< 0.0005
Renal anomaly	91 (15.7)	8 (0.8)	< 0.0005
Radial ray anomaly	57 (9.8)	0 (0)	< 0.0005

TABLE II. Frequency of Other VACTERL Malformations in OA Cases

Number of other					
malformations	0	1	2	3	4
Frequency	330 (57%)	133 (23%)	68 (12%)	32 (6%)	16 (2%)

## **RESULTS**

As previous studies have shown [Barbujani et al., 1989; Robert et al., 1993; Yang et al., 1994], there is little geographical variation of OA cases, and for the purposes of this analysis, we analysed together the data collected from England and Germany. In the OA group there were 360 (62%) males whereas in the control group there were 565 (55%) males; this is in common with previous observations of an excess of male cases of OA [Ein et al., 1989; Depaepe et al., 1993; Harris et al., 1995]. The age range of the cases and controls was very similar (Fig. 1), and most cases and controls were Caucasian (98% in both groups); therefore, samples were treated as if from a single ethnic background.

## **Associated Factors Relating to the Child**

As expected, a large proportion of OA cases had other VACTERL anomalies. Table I shows that all of the other VACTERL components are significantly associated in OA cases when compared with the control group. Table II gives the frequencies of the number of other VACTERL malformations reported to be present in the OA cases; 43% of OA cases presented with at least one other element of VACTERL. Other midline defects have been previously described in association with OA/TOF: for example, cleft lip and palate linked with OA as part of the SCHISIS association [Chittmittrapap et al., 1989] and a range of anomalies in the structures arising from the midline during development, including the spine, heart, gut, and uro-genital tract thought to be the result of weakness of the midline field [Opitz and Gilbert, 1982]. The results of this study confirm emphatically that midline defects (with the exception of neural tube defects) are significantly associated with OA/TOF when compared to the control group, as shown in Table III. Table III also shows that there is a higher incidence of twinning in the OA group compared to the control group. Monozygotic twinning is thought to be an example of a midline defect, and although the zygosity is not known in this study, most twins in the OA group are of the same sex (Table IV) and therefore likely to contain a substantial number of monozygotic twin pairs. In this sample, OA was only present in one of the twins and never in both.

Table V provides a comparison of medical problems which are commonly reported as being associated with OA and some more general childhood problems (i.e., asthma, learning disability, and autism). This study confirms that OA cases are significantly more likely to have an associated medical problem, helping to confirm our hypothesis that OA may form part of a spectrum of disorders. With regard to the more general childhood problems, only learning disability is significantly associated with OA. The term "learning disability" encompasses a number of developmental problems. Possible explanations for such an association include the effect of prolonged hospitalisation during the early years of life, and the long-term effects of chronic ill health [Ludman et al., 1993].

# Comparing Isolated and Associated OA

Isolated OA and associated OA are often considered separately as though they had different causes [Harris et al., 1995; Rittler et al., 1996]. This study does not substantiate this theory, since the isolated OA (n = 330) and the associated OA cases (n = 249) have very similar occurrences of other midline defects and associated medical problems. The exceptions to this are those problems which are often referred to as the "expanded VACTERL association" [Schinzel et al., 1979; Duncan et al., 1991], such as uro-genital anomalies, caudal regression, and failure to thrive, which is more likely to occur in multiply malformed individuals (Table VI). The increased incidence of neural tube defects may represent a more severe end of the spectrum of midline defects in an individual who already has more than one such malformation. Swallowing difficulties were reported in significantly more isolated cases of OA than in associated cases, and this may well reflect the observation that cases with "long-gap" OA are most likely to have oesophageal dysmotility. These cases often represent "pure" OA without TOF, which have been found to be less frequently associated with other anomalies [Ein et al., 1993].

TABLE III. Incidence of Other Midline Defects in the OA and Control Groups

Incidence of other midline defects	OA cases n (%)	Controls n (%)	Odds ratio (95% CI)
Uro-genital tract anomaly	27 (4.7)	7 (0.7)	7.2 (3.1, 16.5)**
Cleft lip and/or palate	11 (1.9)	1 (0.1)	19.9 (2.6, 154.9)**
Other gastro-intestinal malformation	42(7.3)	2(0.2)	40.2 (9.7, 166.9)**
Neural tube defect	5(0.9)	2(0.2)	4.5 (0.9, 23.2)
Sacral agenesis	10(1.7)	0 (0)	**
Sacral dimple	31 (5.4)	9 (0.9)	6.4 (3.0, 13.6)**
Hydrocephalus	9 (1.6)	2(0.2)	8.1 (1.7, 37.7)*
Chromosomal anomaly	8 (1.4)	1 (0.1)	14.4 (1.8, 115.7)*
Twinning	25 (4.3)	8 (0.8)	5.8 (2.6, 12.9)**

<sup>\*\*</sup>P-Value <0.005.

<sup>\*</sup>*P*-Value <0.05.

TABLE IV. Sex Distribution of Twins in OA and Control Groups

	OA cases n (%)	Controls n (%)
Unknown sex/triplet	2(8)	0
Same sex pair	18 (72)	4 (50)
Unlike sex pair	5 (20)	4 (50)

# **Family History**

The study also recorded various aspects of family history of OA and the associated malformations. As it is hypothesised that OA is only one part of the spectrum of the extended VACTERL anomalies, the relatives on whom data were available were classified as either having at least one of the VACTERL associations or none. It would therefore seem sensible to redefine the case group as those index cases who had at least one of the extended VACTERL anomalies: this increased the number of cases to 602 and subsequently reduced the number of controls to 1,008. In order to avoid any bias due to over counting, we analysed only those families who have at least one relative with an anomaly, of the appropriate degree. In addition, when considering presence or absence of a particular condition or problem, for each family we produced an indicator of whether or not one or more relatives of the appropriate degree had the problem.

Considering the first-degree relatives, there are 600 case families and 1,008 control families with at least one first-degree relative with an anomaly. Out of these families 35 (5.8%) case families and 31 (3.1%) control families had at least one first-degree relative with one of the extended VACTERL components. This is significant (P < 0.01), hence supporting the hypothesis that this range of conditions has a genetic contribution. If we consider a sub-set (which should be reliably reported) of the associated defects and medical problems, then Table VII shows that there is a significant association between recurrent respiratory infections in infancy, gastro-oesophageal reflux, and autonomic dysfunction. The latter of these must be viewed with caution as the self-interpretation of autonomic dysfunction (excessive sweating and/or salivation) is very variable and therefore this could be a purely induced significance.

Respondents were asked to list malformations and medical problems in more distant relatives: 191 case families and 187 control families described at least one such relative. In these families 49 (26%) case families and 34 (18%) control families had at least one other relative with one of the extended VACTERL components. This is very nearly significant (P = 0.08) and may represent a poor ability to recall the medical history of more distant members of the family. If one considers associated medical problems and defects in this group, then only swallowing difficulties are significant. However, both recurrent chest infections and gastrooesophageal reflux are very close to significance with *P*-values of 0.7. We would hypothesise that this again is related to the inability to recall relevant medical problems of distant relatives, thus inducing some form of recall bias; in particular for recurrent chest infections it is more likely to be the changing perception of what a recurrent chest infection is across the generations.

#### DISCUSSION

OA/TOF was first described as part of an association labelled VATER by Quan and Smith [1973]. An association has been defined by the International Working Group (IWG), [Spranger et al., 1982] as "the nonrandom occurrence in two or more individuals of multiple anomalies not known to be a polytopic field defect, sequence or syndrome." Furthermore "it refers solely to statistically, not pathogenetically or causally related defects." However, Opitz [1993, 1994] suggests that associations do in fact represent biologically real entities defined as "idiopathic occurrence of multiple congenital anomalies of blastogenesis." The association was renamed VACTERL to include cardiac defects, renal defects (commonly agenesis), and limb defects of the radial ray type [Kaufman, 1973; Nora and Nora, 1975]. The findings in this study are entirely consistent with the previously published reports of these malformations co-existing with OA. In addition, other anomalies of the uro-genital tract and sacral agenesis (caudal regression) can be considered to be part of this association as they occur significantly more often in individuals with OA and VACTERL anomalies, compared to the isolated OA group and the control group. The latter two anomalies are sometimes referred to as the expanded VACTERL association [Schinzel et al., 1979; Duncan et al., 1991]. From a pathogenic point of view, Opitz and Gilbert [1982] suggest that VACTERL anomalies (along with a number of other malformations including monozygotic twinning) are secondary to

TABLE V. Associated Medical Problems in the OA and Control Groups

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	OA cases	Controls	
Associated medical problem	n (%)	n (%)	Odds ratio (95% CI)
Respiratory infections in infancy	35 (6.0)	14 (1.4)	4.7 (2.5, 8.8)**
Respiratory arrest in infancy	11 (1.9)	1 (0.1)	19.9 (2.6, 154.9)**
Gastro-oesophageal reflux	129 (22.3)	1 (0.1)	295.3 (41.2, 2118.7)**
Failure to thrive	67 (11.6)	3(0.3)	44.8 (14.0, 143.3)**
Swallowing difficulties	122(21.1)	10(1.0)	27.3 (14.2, 52.4)**
Autonomic dysfunction	3(0.5)	3(0.3)	1.8 (0.4, 8.9)
Asthma	19 (3.3)	45 (4.4)	0.7(0.4, 1.3)
Learning disability	20 (3.5)	5 (0.5)	7.3 (2.7, 19.7)**
Autism	3 (0.5)	1 (0.1)	5.4 (0.6, 51.7)

<sup>\*\*</sup>P-Value <0.005.

TABLE VI. Comparison of Midline Defects and Associated Medical Problems Between	the Complex OA
and the Isolated OA Groups	

Midline defect or associated medical problem	Isolated OA n (%)	Associated OA n (%)	Odds ratio (95% CI)
Uro-genital tract anomaly	5 (1.5)	22 (8.8)	6.3 (2.4, 16.9)**
Cleft lip and/or palate	5 (1.5)	6 (2.4)	1.6(0.5, 5.3)
Other gastro-intestinal malformation	16 (4.8)	26 (10.4)	2.3 (1.2, 4.4)*
Neural tube defect	0 (0)	5 (2.0)	*
Sacral agenesis	0 (0)	10 (4.0)	**
Sacral dimple	19 (5.8)	12 (4.8)	0.8(0.4, 1.7)
Hydrocephalus	3 (0.9)	6 (2.4)	2.7 (0.6, 10.9)
Chromosomal anomaly	5 (1.5)	3 (1.2)	0.8(0.2, 3.3)
Respiratory infections in infancy	15 (4.5)	20 (8.0)	1.8 (0.9, 3.7)
Respiratory arrest in infancy	5 (1.5)	6 (2.4)	1.6(0.5, 5.3)
Gastro-oesophageal reflux	72 (21.8)	57 (22.9)	1.0(0.7, 1.6)
Failure to thrive	27 (8.2)	40 (16.1)	2.1 (1.3, 3.7)*
Swallowing difficulties	85 (25.8)	37 (14.9)	0.5 (0.3, 0.8)*
Autonomic dysfunction	1 (0.3)	2 (0.8)	2.7 (0.2, 29.5)

<sup>\*\*</sup>P-Value <0.005.

a developmental weakness of the midline. Russell et al. [1981] suggest the term "mesodermal dysplasia syndrome" to link a number of anomalies which could result from defective mesodermal migration. This is thought to be a result of abnormal signalling from the primitive streak to the mesoderm in early embryonic development. However, this definition is probably inadequate as it does not include endodermal anomalies, represented by OA/TOF. It is possible that the root of the problem begins with a dysfunction of the epiblast during gastrulation. Disorders of blastogenesis (i.e., from the point of fertilisation to the end of gastrulation) are thought to account for a number of major malformations described by Opitz [1993]. The list includes such disorders as "conjoined twins"; sirenomelia and all forms of caudal "regression"; anencephaly and spina bifida operta; renal agenesis; anal atresia; tracheooesophageal fistula, tracheal agenesis, oesophageal atresia and vertebral segmentation defects. Opitz noted that all of these malformations occurred with increasing frequency in monozygotic twinning, a condition itself considered to be a defect of blastogenesis. The results confirm an increased incidence of midline defects, including a markedly higher incidence of twinning when compared with the control group, and although the zygosity of the twin pairs is not recorded, most are like-sexed and thus probably monozygotic.

Martínez-Frías et al. [1998] suggest using the term "primary polytopic developmental field defect" to describe some of the conditions previously known as associations such as VACTERL. They argue that

VACTERL and other such conditions are characterised by multi-organ malformations arising from defects in more than one progenitor field during blastogenesis.

As expected, the related medical problems are very common in OA cases. Many explanations have been proposed to account for the presence of these particular problems in this group of individuals. Chest infections and respiratory arrests are thought to be due to a combination of recurrent aspiration (secondary to gastro-oesophageal reflux and/or oesophageal dysmotility) and tracheo-malacia [Dudley and Phelan, 1976; Benjamin et al., 1976; Blair and Filler, 1986; Checuti and Phelan, 1993b]. Swallowing difficulties are attributed to a number of factors including abnormality (inherent or iatrogenically acquired) of the enteric nervous system or vagus nerve [Nakazato et al., 1986; Davies, 1996].

Gastro-oesophageal reflux is often difficult to diagnose, severe, and resistant to drug treatment. The proposed causative mechanisms include mechanical disruption of the lower gastro-oesophageal sphincter and nerve damage thereof due to surgical manoeuvres and possibly abnormalities of the enteric nervous system [Orringer et al., 1977; Ashcraft et al., 1977; Parker et al., 1979; Cheng et al., 1997]. Cozzi et al. [1993] suggest a theory offering a single alternative explanation to all of these problems: disturbances of autonomic function secondary to abnormal neural crest development (neurocristopathy). Cranial neurocristopathies result in the following problems: abnormal autonomic control of sucking and swallowing, reflex apnoea and/or bradycardia, gastro-oesophageal reflux, hyperhydrosis, sial-

TABLE VII. Associations Between First-Degree Relatives With Respect to Midline Defects or Associated Medical Problems

	At least one first degree relative	At least one first degree relative	
Midline defect or associated medical problem	of case with problem n (%)	of control with problem n (%)	<i>P</i> -value
Cleft lip and/or palate	2 (0.3)	5 (0.5)	0.6
Other gastro-intestinal malformation	2 (0.3)	3 (0.3)	0.9
Neural tube defect	2 (0.3)	0 (0)	0.06
Respiratory infections in infancy	49 (8.2)	52 (5.2)	< 0.05
Gastro-oesophageal reflux	59 (9.8)	71 (7.0)	< 0.05
Swallowing difficulties	15 (2.5)	30 (3.0)	0.6
Autonomic dysfunction	32 (5.3)	20 (2.0)	< 0.001

<sup>\*</sup>P-Value <0.05.

orrhoea, and sudden death. Although disturbances of sweating and salivation were specifically queried in the questionnaire, very few respondents admitted to these problems.

The incidences of coincident anomalies and related medical defects are very similar when isolated and associated cases of OA are compared. This indicates that isolated OA may represent one end of the spectrum of malformation combinations, the other extreme being the full spectrum of VACTERL anomalies with additional features such as sacral agenesis.

A number of families have two or more members with OA/TOF. In addition, McMullen et al. [1996] reported the incidence of VACTERL-like anomalies in sibs and offspring of OA cases as being 1.4% and 4.8%, respectively.

This suggests a probable genetic influence in the genesis of OA/TOF. The condition is likely to be polygenic rather than arising from mutations in a single gene. The existence of a spectrum of associated anomalies combined with the finding that OA does occur in families leads to interest in the incidence of these anomalies in other family members. Some VACTERL anomalies are either life threatening and therefore guaranteed to have been diagnosed (e.g., OA/TOF and cardiac defects), or visible such as severe vertebral and radial ray defects. However, defects including renal and mild rib and vertebral anomalies may well go undetected. As a massive screening program would not be ethically acceptable, the true incidence of these anomalies in the relatives will remain unknown. This represents a major limiting factor in a study of this nature. Similarly, the related medical problems described above may be over- or under-diagnosed. The questionnaires rely on information from the children's parents, and whereas to one parent a bad cold with a cough is counted as a chest infection, another may reserve this term to describe an illness requiring hospital admission. Gastro-oesophageal reflux is another condition which is unreliably reported. In this case the reason stems more from the fact that the symptoms of heartburn and acid brash correlate poorly with pH manometry and other objective measurements [Parker et al., 1979; Orenstein et al., 1996].

Another factor to consider is that a family with a child with multiple medical problems will be more aware of similar symptoms in other relatives and may therefore over-report such symptoms. This is particularly true in the case of second- or greater-degree relatives. Bearing these caveats in mind, the results of this study are indicative of a higher than expected incidence of related medical problems in the first-degree relatives, although the incidence of associated malformations is no different than in the control group. Families with numerous members experiencing related medical problems may well prove to be interesting candidates for linkage analysis in an attempt to unravel the genetics of OA/TOF.

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