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Respiratory Care of Infants and Children with Congenital Tracheo-Oesophageal Fistula and Oesophageal Atresia

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EDUCATIONAL AIMS

- To present the epidemiology of tracheo-oesophageal fistula, including incidence, genetic basis, and association with genetic syndromes and other anomalies.
- To present the classification, types, and diagnosis of tracheo-oesophageal fistula.
- To discuss medical treatment and short and long-term clinical outcomes with an emphasis on pulmonary treatment and outcomes.

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SUMMARY

Despite acute respiratory and chronic respiratory and gastro-intestinal complications, most infants and children with a history of oesophageal atresia / trachea-oesophageal fistula [OA/TOF] can expect to live a fairly normal life. Close multidisciplinary medical and surgical follow-up can identify important co-morbidities whose treatment can improve symptoms and optimize pulmonary and nutritional outcomes. This article will discuss the aetiology, classification, diagnosis and treatment of congenital TOF, with an emphasis on post-surgical respiratory management, recognition of early and late onset complications, and long-term clinical outcomes.

INTRODUCTION

Congenital tracheo-oesophageal fistula (TOF) is a relatively common anomaly of the foregut that is associated with acute and chronic respiratory and digestive complications. A TOF consists of an abnormal connection, or fistula tract, between the trachea and the oesophagus, and usually occurs with oesophageal atresia (OA), a congenital malformation in which the upper oesophagus terminates in a blind-ending pouch. Though surgical repair of TOF leads to clinical improvement, some degrees of respiratory, feeding, and gastrointestinal co-morbidities often persist. The clinical presentation, diagnosis, and severity of TOF are variable, and depend in part on the classification type.

Epidemiology and Classification

Tracheo-oesophageal fistulae occur along a spectrum of severity. The majority of TOF (90-93%) occur in association with OA; the latter is the most common congenital malformation of the oesophagus [1–3]. The estimated incidence of OA/TOF is 1 in 3,500 births [4–6] with males having a slight increased incidence, depending on the classification type [7]. TOF and OA/TOF are classified according to anatomic features [Figure 1]. Type A refers to isolated OA, type B to OA with proximal TOF, type C to OA with distal TOF (most common: 85%), type D to OA with proximal and distal TOF, type E (also called "H-type") to isolated TOF without OA, (four to seven percent) [3,8], and type F to congenital oesophageal stenosis [3].

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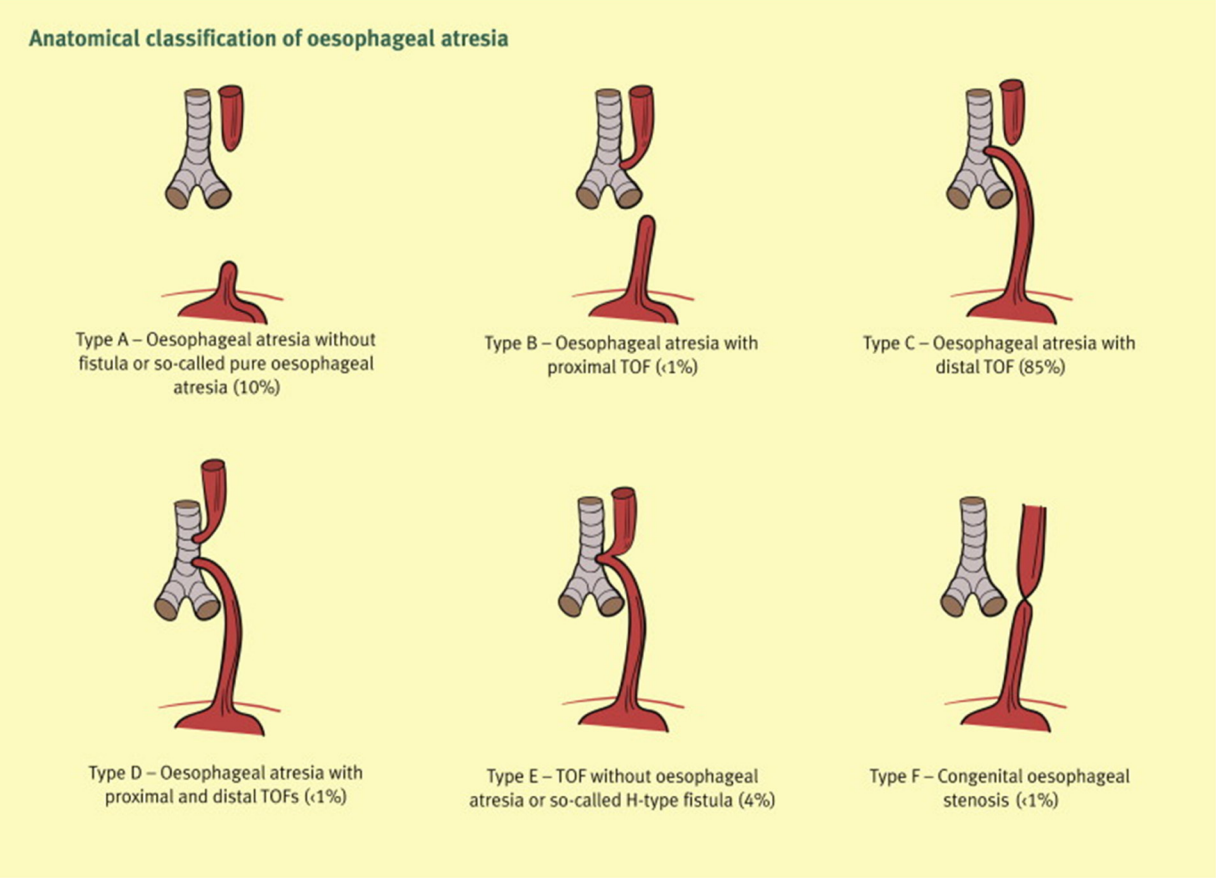

Figure 1. Anatomical classification of oesophageal atresia and tracheo-oesophageal fistula.
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PATHOGENESIS

Foetal Development

OA/TOF develops early in foetal life. The embryologic foregut differentiates into the primitive lung and oesophagus between 22-23 days, and from there, a tracheal/lung bud develops. First an epithelial, then a mesenchymal septum forms to fully separate the respiratory and oesophageal tracts. The division of the respiratory and oesophageal tracts is complete by the time the embryo is six to seven weeks old [9]. In OA/TOF, it is thought that defective epithelial-mesenchymal interactions during early embryologic development leads to improper branching of the lung bud, resulting in a fistula tract between the trachea and oesophagus [10].

Genetic and Environmental Factors

The aetiology of OA/TOF is likely multifactorial, with environmental, genetic, and possibly epigenetic factors involved in its pathogenesis. The familial recurrence rate is low (one percent), and most cases are likely the result of *de novo* mutations [11]. Genetically identical monozygotic twins have a 50% chance of sharing the OA phenotype, while genetically non-identical dizygotic twins have half that risk. Other contributing factors, including environmental exposures, may also be important [12]. Studies of mouse and rat models and also tissue from humans with OA/TOF have implicated a defect in the *Sonic Hedgehog* (*Shh*) signalling pathway and its downstream effectors (including *FOXf1*), which contribute to epithelial/mesenchymal signalling [13]. Recently, a microdeletion that encompasses the FOX transcription gene cluster at 16q24.1, which affects foregut and lung development, has been implicated [13], and other genes specific to defined genetic syndromes have also been identified [14]. Some proposed environmental factors that have been associated with OA/TOF include maternal first trimester exposure to exogenous sex hormones [15], methimazole [16], pesticides and herbicides [17], diabetes [18], and an unknown infection [19]. One case-control study reported a slight increased risk of OA/TOF with maternal smoking or alcohol use during pregnancy [17], but a much larger study did not support this association [20]. Currently, the role of environmental factors in the development of OA/TOF is not completely understood.

Clinical and Syndromic Associations

Most cases of OA/TOF occur spontaneously, and though the defects may be isolated, at least 50% have one or more additional anatomic malformations [21–23]. The most common associated anomalies are those within the VACTERL spectrum (V-vertebral anomalies, A-ano-rectal atresia, C-congenital heart lesions, TE-tracheo-oesophageal defects, and L-limb anomalies) [21]. Congenital heart defects are the most common comorbidity (13-34%) [24]. Some genetic syndromes that are associated with OA/TOF include CHARGE (C-coloboma, H- heart defects, A- choanal atresia, R- retardation of growth and/or development, G- genital and/or urinary defects, E- ear anomalies) syndrome, Feingold syndrome, AEG (anophthalmia-oesophageal-genital) syndrome, and X-linked Opitz syndrome [13,25]. OA/TOF also occurs in association with trisomies, particularly 18 and 21 [24]. A causal mutation associated with a defined genetic syndrome of known aetiology can be identified in up to 11-12% of patients with OA/TOF [11,26].