What causes TOF/OA?

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Is there any pattern to TOF?

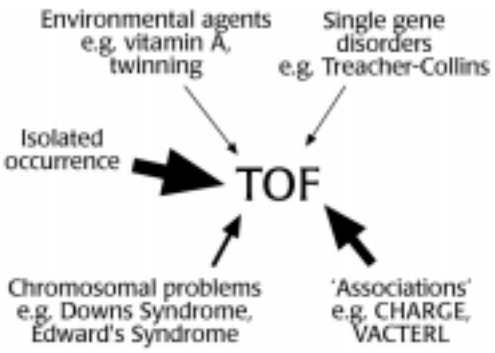
Tracheo-oesophageal fistula (TOF) affects approximately 1 in every 3,000 births.

It can occur in isolation or as part of a variety of different conditions.

One UK study found that just under half the time (45%) TOF occurs in isolation as the only developmental anomaly. In the remainder of instances it occurs together with other congenital anomalies.

Isolated TOF (i.e. TOF without any other anomaly) is a 'one off' occurrence. Where it occurs with other anomalies there is usually an underlying diagnosis, which falls into one of four categories:

i) the commonest is an 'association' such as VACTERL and CHARGE
ii) the next main group is that where there is an underlying chromosome abnormality e.g. Downs syndrome or Edward's syndrome
iii) occasionally TOF is associated with exposure to an environmental agent e.g. excessive vitamin A or maternal alcohol abuse. TOF is also more common amongst twins
iv) very rarely TOF occurs as part of a syndrome specified by a single gene e.g. Treacher-Collins syndrome.



ABOVE:
Diagnostic categories associated with TOF.

RIGHT:
Embryology ... the oesophagus and trachea develop from the primitive foregut during the 6th and 7th week of pregnancy.

Why did it happen?

It is usually not possible to answer this question precisely. Most of the time we do not know why a TOF occurred. However, given the immense complexity of the embryological processes involved in forming a baby it is perhaps not surprising that occasionally one of these processes goes slightly awry.

During the sixth and seventh week of pregnancy, the upper part of the primitive foregut divides lengthways into a digestive tract (oesophagus) and a respiratory tract (trachea). If this process is disturbed, a TOF may occur. The disturbance can be due to one of the situations described above – a genetic or chromosomal problem affecting this stage of development, or exposure to toxic environmental agents – but it is usually not possible to determine exactly why it happened.

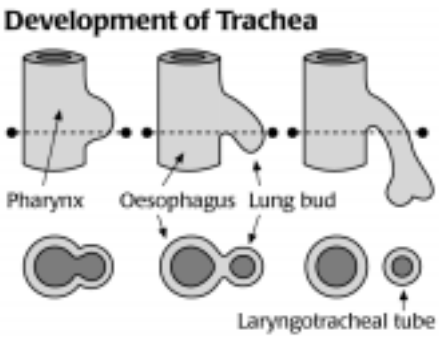
Will it happen again?

Fortunately in the great majority of instances the answer is very reassuring and recurrence is unlikely.

Isolated TOF occurs as a sporadic 'one-off' event and the chances of a recurrence is approximately 1%. Likewise TOFs occurring as part of an 'association' are usually sporadic and also have a low recurrence risk, in the region of 3%.

In the few instances where an environmental agent has been identified, steps can be taken to avoid exposure in a subsequent pregnancy.

It is therefore appropriate to be optimistic about a future pregnancy since the chance of a recurrence of TOF is low.



This information has been written for the parents of TOF children by TOFS (Tracheo-Oesophageal Fistula Support) – helping children born unable to swallow.

If you have any feedback on this leaflet, please use our leaflets feedback form which is available from either the TOFS office our web site.

TOFS relies on money from membership fees, voluntary donations and other sources of charitable income to fund its activities.

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TOFS does not offer specific medical advice to parents. We work only in a supportive role, offering emotional and practical support to meet the needs of parents and providing a source of information which complements that given by the specialist hospital.

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Rarely TOF may be a feature of a rare genetic disorder. It is listed as a feature of more than 20 very rare genetic syndromes. Many of these follow predictable Mendelian inheritance patterns; the recurrence risk is that of the underlying disorder, which is usually high e.g. 25-50%.

Genetic counselling

People often seek genetic counselling to find out more about a specific condition which has occurred in a member of the family. They are referred to a Clinical Genetics Centre by their General Practitioner and will be offered an appointment with either a Clinical Geneticist (a doctor) or Clinical Nurse Specialist in Genetics. During the appointment the counsellor (the doctor or nurse specialist) will often draw a family tree in order to identify any other relative who may be affected by the same condition.

Specialist genetic advice should be sought, but is especially important where:

i) a TOF is not isolated, but occurs in conjunction with other anomalies
ii) more than one individual in the family is affected by TOF.

Can anything be done to prevent a recurrence?

With the exception of TOFs occurring as part of a rare genetic syndrome, the chance of a recurrence of TOF is low.

If the geneticist considers an incidence of TOF to be part of a genetic pattern, he or she will explain the inheritance pattern and recurrence risks to members of the family. In some cases a genetic test may be available (e.g. Treacher-Collins syndrome) and this would be discussed during the consultation.

Detailed anomaly ultrasound scanning by an experienced person can sometimes indicate a TOF antenatally. If there is oesophageal atresia the baby is unable to swallow the amniotic fluid which therefore accumulates. This is termed 'polyhydramnios.' The baby's stomach may also appear small. Absence of these signs may provide reassurance in a subsequent pregnancy.

Research into TOF

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What causes OA/TOF? What causes VACTERL? These questions have no satisfactory answers – all we know is that some factor operates at a specific point in pregancy – when the oesophagus, trachea and the organs affected in VACTERL are forming – such that the processes which lead to the normal development of these structures are disrupted. Just what that factor is we don't yet know.

THE TOFS FAMILY STUDY

Many readers will have participated in the TOFS family study, based on a questionnaire which was sent to TOFS membership (and members of the German support group KEKS) by Dr Andrea Brown at the University of Oxford in 1997/8. This resulted in the publication of a scientific paper with some interesting findings:

Firstly, the study placed OA and TOF at one end of the spectrum of anomalies seen in VACTERL, something which had been suspected but not satisfactorily confirmed. An association with anomalies termed 'midline defects' (e.g. other gastro-intestinal malformations, sacral agenesis, sacral dimple, cleft lip/palate, hydrocephalus, uro-genital anomalies and twinning) was also observed.

Secondly, the study demonstrated that the relatives of TOF children are more likely to have these anomalies than the rest of the population. It is generally held that there is usually no genetic element in OA/TOF/VACTERL, however, the finding that family members of affected children show an increased incidence of these defects suggests that there may be a genetic factor. (It is important to stress that current statistics concerning the likelihood of recurrence for OA/TOF and VACTERL still, of course, hold true; readers are referred to the TOFS leaflet 'What causes TOF?' for information).

Thirdly, not only do the OA/TOF patients have a range of medical problems such as oesophageal dysmotility, reflux and chest infections – their relatives also are more likely to have these problems. This adds weight to the previous suggestion that there may be a genetic 'story' to investigate further.

VITAMIN A AND TOF

Dr Simon Ward, at the University of Sheffield, is a developmental biologist whose main interest is vitamin A. His previous work has shown that rats which have a genetic predisposition to vitamin A deficiency may live normally, however if subjected to a vitamin A deficient diet at specific points during pregnancy will give birth to pups with anomalies similar to those in VACTERL. Both the deficiency

Related leaflets from TOFS which you might like to read:

1. What is TOF/OA?
2. Conditions occurring with TOF/OA
3. VACTERL: an overview

These are all available from the TOFS web site (www.tofs.org.uk) or from TOFS office.

TOFS also publishes a book, 'The TOF Child,' which is suitable for both parents and medical professionals. Details are available from TOFS.

and the genetic predisposition have to be present; this is therefore a 'gene-environment interaction'.

This revelation may leave some readers feeling confused and worried. What does this mean? Did they eat badly? Do they have faulty genes? Should they now supplement their diets with vitamin A?

No, No and NO! It is far, far too early. The research has a long way to go before anyone can say whether this is what causes OA/TOF or VACTERL in humans – and as for supplementation, vitamin A is not only problematic if deficient, it is also toxic in excess, so nobody should be looking to increase their dietary intake.

The exciting possibility nevertheless remains that if this turns out to be true, there may be the potential for genetic tests to indentify 'at risk' individuals and offer supplementation much in the same manner as folic acid is currently given to pregnant woman.

THE ADRIAMYCIN MODEL

It has now been known for some years that if the anticancer drug adriamycin is administered to rats on particular days of pregnancy, a proportion of the litter will be born with OA/TOF. This finding has drawn much interest worldwide, and a number of papers have emerged describing the oesophageal and tracheal abnormalities found (e.g. the nerve supply to the oesophagus) and the presence of other anomalies, such as those in VACTERL.

Researchers believe that this animal model will help our understanding of the problems associated with OA/TOF, such as reflux and oesophgeal dysmotility. They also think that it will increase our knowledge about the cause of these anomalies … if we can understand the way in which adriamycin exerts its effects, we may be led towards similar pathways which operate when these anomalies occur in TOF families.

It's a radically different approach to that which Dr Ward is taking; Dr Ward however feels that whilst work on adriamycin may tell us about the damaging effects of the drug, it may not be relevant to the 'natural' occurrence of OA/TOF in the human population.

OTHER AREAS OF RESEARCH

Other groups are looking at OA/TOF and VACTERL, however we have yet to gather adequate information on their activities on which to base anything nearing even an introductory report.

What we do know is that Dr Ward and his research team are looking at the relationship between reproductive hormones/fertility treatments and OA/TOF, and various groups are carrying out genetic testing on blood samples drawn from TOF families – the newly formed 'TV Network' support group in Australia mentioned in a recent newsletter that parents there have contributed samples to one study, and there are other projects under way elsewhere. So this area of research is attracting a lot of attention; hopefully at some point there will be the opportunity for the various groups to come together and discuss their findings and share their thoughts and expertise.

HOW CAN TOFS MEMBERS HELP?

Our members have already made valuable contributions by participating in the TOFS family study. TOFS is now contributing funds towards the work at Sheffield, so by donating to TOFS funds you are also helping this research.

If other opportunities arise for TOF families to help, we will let you know.

GOT MORE QUESTIONS?

If you have queries or comments relating to research, please contact Julie Byard. You can write to Julie by sending a letter addressed to her at the TOFS office, or email her at research@tofs.org.uk