Oesophageal atresia and malrotation: What association?

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Introduction

Oesophageal atresia with or without tracheo-oesophageal fistula (OA or OA/TOF) is a congenital condition with an incidence of approximately 1:3500 live births. Various different forms have been described, with the most widely used anatomic description being that of Gross (1). The most frequent form is OA in combination with a distal tracheo-oesophageal fistula (Gross Type C), with others including: isolated OA (type A), OA with proximal tracheo-oesophageal fistula (type B), OA with both proximal tracheo-oesophageal fistulae (type D) and TOF with no atresia (type E; H-type). There are many described associations with the most common being the VACTERL association (Vertebral defects, Anal atresia, Cardiac defects, Tracheo-(o)Esophageal fistula, Renal malformations, and Limb defects) which should be investigated for in any baby presenting with OA/TOF. The syndromic forms of OA/TOF are reported to occur in approximately 50% of patients and usually involve a cardiac anomaly. (2)

Malrotation is a congenital abnormality that manifests as abnormal bowel configuration. During the 6^{th} week of gestation the intestine is described to herniate into the putative umbilical cord and return into the abdomen rotating 270 degrees anticlockwise as it does so. It then lies in the usual configuration with a wide based mesentery fixed to the retroperitoneum. In malrotation this re-entry into the abdominal cavity is misguided resulting in a spectrum of abnormal positioning and fixation of the bowel. In its worst form, the small bowel mesentery is narrow and the midgut can rotate on its pedicle leading to volvulus with obstruction of the arterial inflow and venous outflow. This can result in loss of the entire midgut due to ischaemia and necrosis. Post-mortem studies (3) and radiological studies on the position of the caecum (3) give the overall incidence of malrotation as being 1:200 to 1:500. However, there is no indication of whether any, some or all of those patients were symptomatic. Most malrotations, presumably, remain asymptomatic. Although Marx (4) attempted to divide malrotation into sub-types which were at risk of volvulus or not, they are often difficult to determine clinically and radiologically. The resultant diagnostic uncertainty and potential catastrophic outcomes of death and severe short bowel syndrome if volvulus occurs often preclude expectant management of any patients with an upper gastro-intestinal contrast study (UGIS) showing malrotation.

In lieu of these difficulties we attempted to define the incidence of malrotation in OA/TOF patients at a single institution. The literature defines the overall incidence of malrotation in OA/TOF as 3-5%, (5, 6) with some studies reporting the number of patients who had a upper gastrointestinal contrast study (UGIS) and some detailing the presence or otherwise of associated symptoms. There is no literature detailing the incidence of malrotation in particular types of OA/TOF which this paper aims to address.

Methods

A retrospective review of prospectively collected data was performed of all patients admitted to our institution between April 1981 and January 2013 with a diagnosis of oesophageal atresia and/or trachea-oesophageal fistula. This included patients who had their primary procedure at another hospital or who were referred to any specialty at our institution. Patients who had a diagnosis of malrotation were also reviewed and the two groups cross-referenced.
OA/TOF anatomical category according to the Gross classification, symptomatology, UGIS images and operative procedures performed were reviewed.
Numbers were compared against the best evidence available for the prevalence of malrotation.
Statistical analysis was performed using Graph Pad Prism 6 (Graph Pad, San Diego, CA) and figures are median (range) unless stated. Fishers exact test was used for statistical interpretation with a P value of <0.05 taken as significant.

Results

Total number of patients identified with OA/TOF and who had confirmation of duodeno-jejunal flexure (DJF) position by UGIS, laparotomy/laparoscopy or post-mortem was 235.
Of these, 28 were Gross type A (12 %), 196 type C (83%), 2 type D (1 %) and 9 type E (4 %).
There were 3 patients with type A OA/TOF who had malrotation, comprising 2 who had the diagnosis made on UGIS and one who underwent laparotomy for suspected jejunal atresia, but was found to have a malrotation and volvulus.
There were 6 patients with type C OA/TOF who had malrotation. Four were diagnosed on pre-operative UGIS as work up for a gastrostomy insertion and/or fundoplication. One was diagnosed at surgery for duodenal atresia, and the other at surgery for a pyloroplasty, who was noted to have an unfixed caecum and malrotation and so a Ladd's procedure was performed.
There were no patients in the type B, D, or E OA/TOF groups who were diagnosed with malrotation.
In total, 9/235 (3.8%) patients had malrotation. In view of the small numbers of patients with malrotation, we have calculated the 95% confidence interval of this proportion, which is 2.0-7.2%. This figure is significantly higher than the 5/1050 (0.48%) reported in post-mortems ($p=0.0002$) (3)
In the type A group, 3/28 (11%; 95% CI 3.7-27.2) had malrotation, which was also significantly higher than the reported incidence (Smith; $p=0.0008$). In the type C group, 6/196 (3%, 95% CI 1.4-6.5%) had malrotation, significantly higher than the incidence reported by Smith ($p=0.0033$,) but not significantly different to the type A group ($p=0.0878$).
Co-morbidities of patients with OA and malrotation are shown in Table 1.

Discussion

OA/TOF is a well-recognised congenital abnormality with very good evidence of its prevalence and a definitive investigation and management plan. Although controversies exist in its embryological origins, the fundamental morphogenetic processes are well recognised. (7) The consequences of not treating it are profoundly deleterious to the patient.

In contrast, malrotation is a more nebulous condition. Its embryological origins are uncertain and, despite general acceptance of its anatomical development, unproven (8).

The management of symptomatic malrotation is a Ladd's procedure, but the management of asymptomatic malrotation is unclear. Whether to perform a prophylactic Ladd's procedure continues to be a matter or great debate because of its well established relationship to midgut volvulus, which can cause significant morbidity and mortality.

Estimates of its prevalence vary greatly and the definitive answer of which patients with malrotation are susceptible to volvulus remains elusive.

The best estimates at prevalence come from work done a century ago in 1910 by Smith (3) who undertook post-mortems in 1050 children and discovered 5 patients with left sided and unfixed large bowel with a narrow small bowel mesentery. These clearly fit the contemporary definition of malrotation, but his study does not elaborate on the causes of death in these patients. Kantor (4) looked at contrast enema studies and determined the position of the caecum and appendix which was abnormal in 1 in 500 patients.

Marx (5) described malrotation, nonrotation and inverted rotation, but ascertained that they were all at risk of volvulus. Contemporary authors disagree alluding that the bowel in nonrotation is not at risk of volvulus and, that in any case, following the Ladd's procedure, the bowel is placed in nonrotation. However, volvulus is still possible with nonrotation and depends on the degree of fixation to the posterior abdominal wall. Millar reports such a case in a child with Beckwith Wiedeman syndrome (10)

Those with a fixed caecum are at low risk of volvulus, but categorising as "low-risk" an abnormality which can cause significant bowel loss and death is difficult. There will always be the patient who disproves the rule, but the risk to benefit ratio of performing a Ladd's procedure in an asymptomatic patient is debatable.

Mehall (11) showed that patients with asymptomatic or atypical malrotation have a higher rate of morbidity due to complications. These outcomes are mirrored by those of Papillon (12) who looked at patients with heterotaxia undergoing Ladd's procedures and found that the incidence of complications was higher in those who had asymptomatic malrotation. Malek (13) in an elegant decision tree analysis showed that the number of quality adjusted life years (QUALY's) justified a Ladd's procedure up until the age of 19.8 years in asymptomatic malrotation diagnosed outside infancy. Mehall and Schey (11,14) independently attempted to develop risk stratification schemata based on the ligament of Trietz and the position of the caecum, but these have not been independently verified or gained wide usage. Hsiao (15) in 2011 advocated the use of laparoscopy in equivocal cases to assess the base of the mesentery and proceed to a Ladd's procedure if abnormal with good results and minimal complications.

This study raises a number of questions, not least; at what level of prevalence do we investigate for associated anomalies. Clearly we cannot hope to answer that within the remit of this paper, but relevant examples include: testing for cystic fibrosis (CF) in patients with rectal prolapse (~4% of patients with CF present this way), investigations for VACTERL association, CHARGE association, neoplastic disease in Beckwith-Weidemann (estimated risk for overall tumor development is 7.5 (range 4-21)%)(16), Wilms in WAGR and Denys-Drash. In patients with these conditions, investigations for specific associated conditions are a standard of care as they can cause significant morbidity.

In Ashcrafts (17) international book on paediatric surgery it is quoted that in combination with OA/TOF, "Of the gastrointestinal anomalies, the most frequently encountered are duodenal atresia and malrotation, and, in addition, there is an increased incidence of pyloric stenosis found."

In Puri and Höllwarths (18) text on paediatric surgery it reminds us that "The most common gastrointestinal associated anomaly [with OA/TOF] is anorectal atresia (9%), followed by duodenal atresia (5%), malrotation (4%), and other intestinal atresia (1%)."

Uphadayay (6) looked at all OA/TOF patients and found that of 60 who had had a contrast study, 3 had malrotation thus giving a figure of 1 in 20 (5%) which is comparable with our series whose overall total was 1 in 26 (3.8%). However, they did not split their patients into specific OA groups. de Jong (19) et al, looked at non-VACTERL anomalies in OA/TOF patients and recorded a 3.3% incidence of malrotation. Stoll et al (20), had 3 patients from 99 with malrotation, again around a 3% incidence. Cieri et al, (7) investigated an active surveillance registry of structural birth defects over 11 years and found an incidence of malrotation of 4.4% in OA/TOF patients. This study also found that patients with OA and malrotation had a generally higher prevalence of other GI anomalies compared to those who had normal rotation. Within the malrotation group there was a prevalence of 40% with anal atresia/imperforate anus, 43% with duodenal atresia, almost 80% with cardiac defects, 40% with CNS anomalies excluding hydrocephalus and almost 40% with genital defects in both the male and female groups. They suggested that these infants have a more serious developmental insult than those without malrotation. We did not specifically look for this in our study and further research in this area would be beneficial.

Many of these studies use anomaly databases in order to identify patients and thus there is a potential under-reporting of cases and this should be borne in mind when appraising these results. Only this paper and that of Uphadayay (6) specifically assessed the DJF in order to diagnose malrotation.

Our series has found a malrotation incidence of 11% in the group with Gross type A, a previously unreported association. This high number may be in part due to the syndromic nature of patients with pure OA. It is interesting to note that malrotation is genetically associated with OA (21), specifically with Martinez-Friaz and microgastria-limb reduction defects. TOF has been associated with malrotation in a ZIC3 abnormality of left to right patterning (21). Malrotation has been described in combination with OA in Feingold syndrome (22)

Malrotation is not the only anatomical abnormality to be reported as having an increased incidence in those children with OA. Pyloric stenosis has recently been shown to have a 7.5% incidence in OA/TOF patients (23) which is 30 times higher than the 0.25% incidence recorded in the general population (24). This increase did not correlate with type of OA.

Other anomalies are well documented and include those in the VACTERL association along with duodenal and other small bowel atresias.

Clearly, there are limitations to our retrospective study. We excluded patients who did not have radiological, operative or anatomical assessment of the position of the DJF and given the international referral pattern to our institution, it is feasible that some patients may have gone on to have imaging and/or surgery elsewhere. However, the overall incidence of patients with malrotation in our study are comparable to those published elsewhere (Table 2) giving credence to the figures contained within this paper.

We conclude that there is a high incidence of malrotation in patients with pure oesophageal atresia. We recommend identification of the DJF position at initial gastrostomy placement where feasible or a low threshold for an upper GI contrast study in these patients via the gastrostomy, orally or via naso-gastric tube following oesophageal anastomosis.

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Table

Type of OA/TOF	How malrotation identified	Co-morbidities
OA with distal TOF	UGIS prior to gastrostomy insertion	GOR, ano-rectal malformation, infantile PCKD
OA with distal TOF	UGIS during assessment for GOR	Atrial isomerism
OA with distal TOF	UGIS during assessment for GOR	None
OA with distal TOF	At surgery for duodenal atresia	Single kidney, polydactyly, duodenal atresia
OA with distal TOF	At surgery for pyloroplasty	Duodenal stenosis, annular pancreas
OA with distal TOF	UGIS during assessment for GOR	PDA, ASD
Isolated OA	UGIS during assessment for GOR	ASD, congenital CMV
Isolated OA	UGIS during assessment for GOR	None
Isolated OA	At laparotomy for suspected jejunal atresia	Micropthalmos, hypospadias

*UGIS – Upper gastrointestinal contrast study, GOR – gastro-oesophageal reflux, PCKD – Polycystic kidney disease, PDA – patent ductus arteriosus; ASD – atrial septal defect; CMV – Cytomegalovirus

Table

Study	Cieri et al. 1999	de Jong et al 2008	Stoll et al 2009	Uphadyay et al. 2001	Pachl et al. 2014
Total OA patients	632	90	99	90	235
Total who had documented DJF assessment	0	0	0	60	235
Abnormal DJF	28	3	3	3	9
OA with malrotation (%)	4.4	3.3	3	5 (of those who had UGIS)	3.8

*UGIS – Upper gastrointestinal contrast study; DJF – Duodeno-Jejunal flexure; OA – Oesophageal atresia

Table legend

Table 1. Patient characteristics

Table 2. Comparison of papers