**Should All Babies With Oesophageal Atresia Have Routine Screening For Midgut Malrotation Anomalies? A Systematic Review In Search Of Evidence.**

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Reprints will not be available from the author.

Funding – No funding to declare

Word Count = 1470

Figure Count = 1

Table Count = 3

Running Head: Esophageal atresia intestinal malrotation screening

**Structured Abstract**

Background/Purpose: Oesophageal Atresia (OA) is associated with co-existent anomalies. There is a controversy of literature pertaining to the risk(s) of intestinal malrotation. In order to guide management we critically evaluate the incidence of IM anomalies in OA newborns.

Design: MEDLINE and EMBASE databases were searched using keywords “(O)Esophageal Atresia and Malrotation/Associated Abnormalities/Associated Anomalies”. Full texts of articles were screened if manuscripts exclusively reported patients with OA malrotation and/or associated anomalies. Larger case series (> 10patients) were included if abstract(s) showed that associated anomalies were systematically assessed. Full eligibility criteria required at least one case of malrotation in an OA index case. Data were collected on article type, number of patients and method(s) of diagnosis.

Results: 632 abstracts were screened of which 158 papers were analysed based on inclusion criteria - 30 manuscripts documented the incidence (%) of malrotation. Incidence rate(s) were 0.5% - 13%. Malrotation was observed to have a higher incidence (10% - 44%) in OA babies with other gastrointestinal anomalies (VACTERL).

Conclusion: Newborns with OA appear to be at a higher risk (%) of having intestinal malrotation anomalies than healthy babies. Prospective studies are required to accurately quantify and define the ‘ true incidence ‘ of this association. Given the potential lethal consequences of midgut volvulus screening may be justified in OA babies. Consensus guidelines (DELPHI) exploring surgeons attitudes with regards management of ‘ asymptomatic malrotation ‘ disorders in OA newborns may further guide best practice.

KEY WORDS: Oesophageal Atresia ; Malrotation ; newborn

Level of Evidence IV – Due to study design of manuscripts included.

1. **Introduction**

Oesophageal Atresia (OA) is one of the most noteworthy index paediatric surgical disorders. Since the first successful repairs were undertaken in the 1940’s , advances in neonatal medicine, operative technique(s) and post-operative care have dramatically improved outcomes for these patients such that morbidity and mortality is now mainly linked to co-associated anomalies such as lethal chromosomal phenotypes or severe structural cardiac malformations (1).

Oesophageal atresia is an isolated condition in just over 53% of cases, with remaining patients often having at least one associated anomaly or condition(2). The commonest associated anomalies may form part of the VACTERL (Vertebral, Anorectal, Cardiac, Tracheoesophageal Fistula, Renal and Limb) spectrum . Approximately 8% of children with oesophageal atresia may have a chromosomal abnormality,- Trisomy 18 (Edward’s syndrome) perhaps being the most well known (3).

Recent reports have emerged suggesting that oespophageal atresia may be associated with a higher incidence of intestinal malrotation disorders than that observed in the healthy population (3–5). Malrotation is linked to failure of the gut to undergo a normal pattern of rotation exhibiting an anticlockwise course as it returns to the abdominal cavity after the normal physiological herniation seen in the first trimester(6). Malrotation has an estimated incidence of 1:500 cases in the general population on the basis of post mortem studies(7). Whilst malrotation may remain ‘ asymptomatic ‘ , risk(s) include midgut volvulus around the fore-shortened mesentery. This can be a fatal event with catastrophic mid gut infarction , or even when emergent surgical management is timely may be linked to survivors experiencing short bowel syndrome with a significant morbidity including requirement for intestinal transplantation. Subsequently, whilst there remains debate on the management of ‘ asymptomatic malrotation ‘, many surgeons nonetheless advocate early surgical intervention to mitigate these risks.

Against this background, this study aimed to critically review current published studies to more accurately define the incidence of intestinal malrotation anomalies in oesophageal atresia patients , with the objective to help determine ( i ) if routine screening of midgut anatomy is warranted and ( ii ) prophylactic Ladd’s operative correction.

1. **Methods**

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines(8). Using the UK NHS Healthcare Databases Advances Search tool, MEDLINE and EMBASE were searched for ALL articles using the terms “(O)Esophageal Atresia” AND “Malrotation”, “Associated Anomalies” OR “Associated Abnormalities”. There were no time or year limits on the search, which was completed in June 2020. References of included studies were also screened to maximise eligible papers.

*Eligibility Criteria*

Papers were eligible for inclusion if they defined a patient cohort (or detailed subgroup analysis) of oesophageal atresia cases only and were English language papers. Papers had to include at least 10 index OA cases with complete description of the associated anomalies in the cohort studies. Animal studies and isolated case reports were excluded. Further analysis of referenced papers was then undertaken if considered of relevance by the study investigators.

*Outcome Measure(s)*

An incidence rate (%) of malrotation was calculated where applicable from the information contained in the screened eligible papers.

*Data Collection*

An electronic database was created (PG), tested on randomly selected articles then adjusted for final validity to a second reviewer. Following removal of duplicate articles, two authors (PG and CN) independently screened all abstracts and eligible papers. Any disagreements were settled by consensus. Studies were then finally approved by the senior author (PDL). Methodological and reporting quality was assessed using the MINORS criteria tool (9). For each published study, data were collected on Authors, Journal published by, year, the incidence (%) of midgut malrotation and the methodology / results in the publications in which malrotation was reported.

*Statistics*

Correlations were assessed using Spearman’s rho test, with p<0.05 taken as significant.

1. **Results**

After duplicate removal from the database searches, 632 abstracts were screened, 158 original papers were scrutinized and 30 papers then selected with filters for full review.- Figure 1.

Table 1 illustrates demographic information from selected papers as well as the studies. Twenty nine out of thirty papers were retrospective cohort study reviews. Twenty two out of thirty studies (73%) were single-centre retrospective case series. Table 2 highlights the incidence (%) of malrotation reported in oesophageal atresia patients, with rates varying between 0.5 %- 13%. In the majority of papers, intestinal malrotation disorders were listed in a Table of patient co-morbidities with no clear documentation on the method of diagnosis or if an operation was undertaken to correct the anomaly. Only two papers, *Pachl et al* (2015)(4) and *Upadhyay* *et al (2001)* (5) specifically investigated and documented the anatomical position of the duodeno-jejunal flexure and the estimated incidence of malrotation. The incidence rates remained unchanged over time (rho=-0.06, p=0.74).

*Study Quality*

Figure 2 summarises the MINORS methodological index scores for the included papers. In general, studies scored highly for documenting the defined aims and for including consecutive patients however were penalised for their retrospective nature and / or the lack of a pre-determined study size.

1. **Discussion**

To the best of our knowledge, this is the first systematic review to make effort to accurately determine the incidence (%) of intestinal malrotation in oesophageal atresia patients. During the last 50 years or so a number of publications have suggested that oesophageal atresia babies may have a higher incidence of anomalies of gut rotation compared to the healthy general population. Malrotation is well known to have a higher incidence (%) in other congenital gastrointestinal malformation disorders including anorectal malformations(10) and duodenal atresia(11). We reviewed two studies here which included patients with oesophageal atresia and anorectal malformations(12) and duodenal atresia(13) respectively. The incidence rates of intestinal malrotation were 3.6% and 10% respectively much higher than that seen in the healthy general population.

*Pachl et al (2015)*(4)noted an association between oesophageal atresia Gross classification Type A and intestinal malrotation (11%) speculating an increased incidence of syndromic anomalies with isolated ‘ pure ‘ oesophageal atresia. We further uncovered a single paper that specifically reported additional data on patients with isolated ‘ pure’ oesophageal atresia. (*Burjonrappa et al (2010)* (14)*)*, showed a notably higher incidence of intestinal malrotation (6.6%) in their study series . Although these published studies may have elements of potential selection bias they nonetheless collectively demonstrate a higher incidence of malrotation compared to the normal healthy population. Efforts were made to explore and assess for this association in other papers, however malrotation was often listed here in a post of co-morbidities and as such it was impossible to accurately state what other anomalies the children in question had here.

Limitations of the current systematic review herein reflect heterogenicity of the available published literature (Figure 2). Future prospective studies ideally would involve screening all index oesophageal atresia babies with midgut contrast radiology imaging prior to hospital discharge after primary repair.

The big question - What to do about patients with oesophageal atresia and ‘ asymptomatic ‘ intestinal malrotation, particularly when the evidence for the best management of ‘ asymptomatic malrotation ’ is lacking. Although the lifetime risk of volvulus in malrotation is not truly known, some authors estimate it to be as high as 20% (15). In the study authors’ experience, many paediatric surgeons may feel that the risks associated with midgut volvulus warrant a Ladd’s operation to counter these dangers whilst accepting there may also be a 10%-25% morbidity linked to future adhesional obstruction. However, in consensus guidelines developed by *Graziano et al*(16)*,* it has been suggested that surgical correction be considered for young patients found to have malrotation (Oxford level of evidence 3-4, recommendation grade C), whilst older patients, or those with ‘ atypical ‘ malrotation, where the duodenojejunal junction is orientated to the left of the midline but below the pylorus may observed, but only if ‘ reliably ‘ diagnosed. Until there are established consensus guidelines on how to best manage oesophageal atresia patients if malrotation is incidentally discovered, it may be difficult then to propose health care recommendations on obligatory screening. Though, in babies with oesophageal atresia, intestinal malrotation does appear to meet WHO criteria for screening - Table 3. Various imaging modalities are available in clinical practice. The current gold standard and the one most readily employed at our surgical centre is upper GI fluoroscopy as the proposed investigation here of choice(17).

In conclusion this systematic review study demonstrates that newborns with oesophageal atresia appear to be at a much higher risk of having intestinal malrotation anomalies than otherwise healthy babies. Given the potential lethal consequences of midgut volvulus radiology midgut screening may be wholly justifiable in babies with oesophageal atresia prior to primary hospital discharge. Consensus guidelines developed in partnership with parent charity support associations such as TOFS UK ( est. 1982 ) or the Federation Of Esophageal Atresia (EAT) may greatly help define ‘ best practice ’ in the future.

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**Funding**

No funding declared

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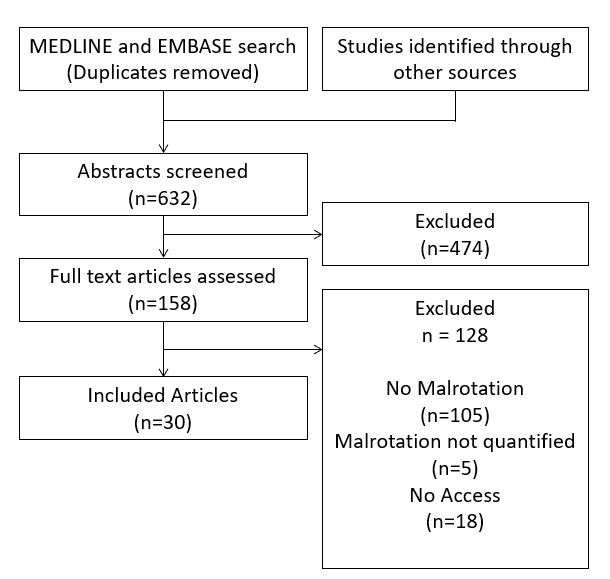
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**FIGURE 1 – FLOW DIAGRAM OF STUDY DESIGN AND PROCESS.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Name** | **Year** | **Journal** | | **Study Type** | | **Institution** | |
| German J.C(18) | 1976 | Journal of Pediatric Surgery | Retrospective Case Series | | Single Centre | |  |
| Kimble R.M(19) | 1997 | Pediatric Surgery International | Retrospective Case Series | | Single Centre | |  |
| Dave, S(13) | 2004 | Pediatric Surgery International | Retrospective Case Series | | Single Centre | |  |
| Andrassy, R J(20) | 1979 | Archives of Surgery | Retrospective Case Series | | Single Centre | |  |
| Friedmacher F(21) | 2017 | Journal of Gastrointestinal Surgery | Retrospective case series | | Single Centre | |  |
| Burjonrappa S(14) | 2010 | Journal of Pediatric Surgery | Retrospective Case Series | | Single Centre | |  |
| Teich S(22) | 1997 | Journal of Pediatric Surgery | Retrospective Case Series | | Single Centre | |  |
| Spitz L(23) | 1987 | Journal of Pediatric Surgery | Retrospective Case Series | | Single Centre | |  |
| Upadhyay V(5) | 2001 | European Journal Pediatric Surgery | Retrospective Case Series | | Single Centre | |  |
| Cieri M.V(24) | 1999 | Teratology | Retrospective Case Series | | Population Registry Data | |  |
| Pachl M(4) | 2014 | Pediatric Surgery International | Retrospective Case Series | | Single Centre | |  |
| Fernandez E(12) | 2014 | Pediatric Surgery International | Retrospective Case Series | | Single Centre | |  |
| Stoll C.(25) | 2017 | American Journal of Medical Genetics | Retrospective Case Series | | Population Registry Data | |  |
| Jong, E.M.G.J. De(26) | 2008 | Birth Defects Research (Part A) | Retrospective Case Series | | Multicentre (n=2) | |  |
| Stoll C.(3) | 2009 | European Journal of Medical Genetics | Retrospective Case Series | | Population Registry Data | |  |
| Brereton R.J(27) | 1978 | Archives of Disease in Childhood | Retrospective Case Series | | Single Centre | |  |
| Driver C.P(28) | 2001 | Journal of Pediatric Surgery | Retrospective Case Series | | Single Centre | |  |
| Engum S.A(29) | 1995 | Archives of Surgery | Retrospective Case Series | | Single Centre | |  |
| David TJ(30) | 1975 | Journal of Medical Genetics | Retrospective Case Series | | Multicentre (true number is difficult to ascertain) | |  |
| Louhimo I(31) | 1983 | Journal of Pediatric Surgery | Retrospective Case Series | | Single Centre | |  |
| Bishop P.J(32) | 1985 | Journal of Pediatric Surgery | Retrospective Case Series | | Single Centre | |  |
| Pini Prato A(33) | 2015 | Journal of Pediatric Surgery | Prospective Observational Study | | Multicentre (n=52) | |  |
| Van Heurn L.W.E(34) | 2002 | Pediatric Surgery Intenational | Retrospective Case Series | | Multicentre (n=3) | |  |
| Poenaru D(35) | 1993 | Surgery | Retrospective Case Series | | Single Centre | |  |
| Ein S.H(36) | 1989 | Journal of Pediatric Surgery | Retrospective Case Series | | Single Centre | |  |
| Chittmittrapap S(37) | 1989 | Archives of Disease in Childhood | Retrospective Case Series | | Single Centre | |  |
| Deurloo, J A(38) | 1992 | Acta Pediatrics | Retrospective Case Series | | Single Centre | |  |
| Li, Xiao-Wen(39) | 2017 | Medicine | Retrospective Case Control Study | | Single Centre | |  |
| Galarreta, CL (40) | 2020 | Am J Med Genet | Retrospective Case Series | | Single Centre | |  |
| Lejeune, S (41) | 2020 | Acta Paediatr | Retrospective Case Series | | Single Centre | |  |

**TABLE 1 – STUDY CHARACTERISTICS**

|  |  |  |  |
| --- | --- | --- | --- |
| **Name** | **Year** | **No of Patients** | **Malrotation Rate** |
| German J.C(18) | 1976 | 102 | 13% |
| Kimble R.M(19) | 1997 | 10 | 10% |
| Dave, S(13)⁺ | 2004 | 10 | 10% |
| Andrassy, R J(20) | 1979 | 150 | 8.7% |
| Friedmacher F(21) | 2017 | 109 | 7.3% |
| Burjonrappa S(14)\* | 2010 | 15 | 6.6% |
| Teich S(22) | 1997 | 94 | 6.3% |
| Spitz L(23) | 1987 | 148 | 5% |
| Upadhyay V(5) | 2001 | 60 | 5% |
| Cieri M.V(24) | 1999 | 632 | 4.4% |
| Pachl M(4) | 2014 | 235 | 3.8% |
| Fernandez E(12)† | 2014 | 167 | 3.5% |
| Stoll C.(25) | 2017 | 116 | 3.4% |
| Jong, E.M.G.J. De(26) | 2008 | 90 | 3.3% |
| Stoll C.(3) | 2009 | 99 | 3% |
| Brereton R.J(27) | 1978 | 158 | 3% |
| Driver C.P(28) | 2001 | 134 | 3% |
| Engum S.A(29) | 1995 | 227 | 2.6% |
| David TJ(30) | 1975 | 345 | 2.6% |
| Galarreta, CL (40) | 2020 | 48 | 2.4% |
| Louhimo I(31) | 1983 | 500 | 1.6% |
| Bishop P.J(32) | 1985 | 271 | 1.5% |
| Pini Prato A(33) | 2015 | 146 | 1.3% |
| Van Heurn L.W.E(34) | 2002 | 82 | 1.2% |
| Poenaru D(35) | 1993 | 95 | 1% |
| Ein S.H(36) | 1989 | 97 | 1% |
| Chittmittrapap S(37) | 1989 | 253 | 0.8% |
| Lejeune, S (41) | 2020 | 157 | 0.6% |
| Deurloo, J A(38) | 1992 | 197 | 0.5% |
| Li, Xiao-Wen(39) | 2017 | 198 | 0.5% |

**TABLE 2 – STUDY RESULTS**

⁺Only included patients with OA-TOF and Duodenal Atresia. \*Only included patient with Gross Type A Oesophageal Atresia-TOF. † Only included patients with OA-TOF and Anorectal malformations.

**FIGURE 2 – MINORS SCORE FOR INCLUDED STUDIES**

|  |  |
| --- | --- |
| **WHO Screening Principal** | **Application to Malrotation** |
| The condition should be an important health problem | Malrotation volvulus can have catastrophic consequences |
| There should be a recognisable latent or early phase | Malrotation in the absence of volvulus |
| The natural history of the condition, including development from latent to declared disease should be adequately understood | Well documented pathophysiology |
| There should be an accepted treatment for patients with the disease | Ladd’s procedure (debate over whether open or laparoscopic is superior) |
| There should be a suitable test or examination that has a high level of accuracy | Upper GI Contrast is gold standard. |
| The test should be acceptable to the population | Upper GI Contrasts are standard investigations in most paediatric surgical units. |
| There should be an agreed policy on whom to treat | Debateable – see main body of text. |
| Facilities for diagnosis and treatment should be available. | Available in all tertiary centres |
| The cost of screening (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole | Upper GI Contrast - £548  Ladd’s Procedure – £4166  Cost of Home PN in the case of short bowel syndrome - £60000-80000 / year(42) |
| Screening should be a continuous process | Arrangements for this already in place |

**TABLE 3.**