PRE-EXISTING NEURAL FACTORS THAT CONTRIBUTE TO DYSMOTILITY IN OESOPHAGEAL ATRESIA: A SYSTEMATIC REVIEW

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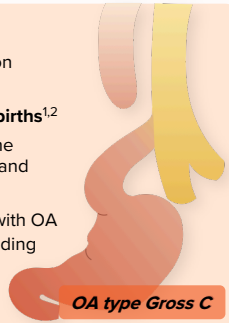
Reference list

Background

- **Oesophageal atresia (OA):** most common oesophageal congenital abnormality
- Overall global prevalence **2.4/100,000 births**[1,2]
- The exact mechanism of separation of the embryonic foregut into the oesophagus and trachea is not currently known.[3]
- Following surgical repair, patients born with OA may experience feeding difficulties including dysphagia, as a result of **dysmotility**.[4]



OA type Gross C

Aim: *To summarise the literature on neuronal & histological pathophysiological mechanisms of oesophageal dysmotility.*

Methods

Protocol submitted to PROSPERO (CRD42020171014)

Literature Search

- General search terms :
  - **'oesophageal atresia'**
  - **'neurology'** / **'histology'**
- Eligible to include : published in **English** & **full-text**

Study Selection:

Screening following PRISMA

- performed by two reviewers
- discrepancies resolved third reviewer

Data Extraction

- General information
- Subject characteristics
  - number of subjects,
  - Gender & age,
  - undergone surgical,
  - types of OA
- Histochemical staining
- Origin of sample
- Objects observed

Quality Assessment:

- SYRCLE scale
- Newcastle-Ottawa scale (NOS)
- Assessment Tool from NHLBI

Results

Study Characteristics

Undergone Surgery?	OA Types	Origin of Sample
Yes (10)	Gross C (9)	TOF (3)
No (1)	Not recorded (2)	Oesophageal Pouch (3)
Not Recorded (1)	Others (3)	Both (6)
**Characteristics & findings could be more than the quantity of study as some studies observe >1 object*	Gross C (3)	TOF (2)
	Not recorded (3)	Oesophageal Pouch (3)
	Type A (1)	Both (1)

Human Studies: Histological tissue (autopsies/ surgical), majority born full term

Animal Studies: Wistar rats (2) & Sprague- Dawley rats (4) received Adriamycin (ADR)

PRISMA Flowchart

Identification
From database searching & additional records
(n = 1105 + 487)

Screening
Record after duplicates removed
(n = 1072)

Eligibility
Full-text assessed
(n = 107)

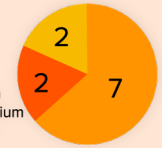
Excluded with reasons (n=78)
- No Full-text (n=16)
- Not histological study (n=12)
- Not focusing on oesophageal dysmotility (n=29)
- Not covering pathophysiology of dysmotility (n=29)
- A case-report or review study (n=8)

Synthesis included for synthesis (n = 18)

1 cross-sectional (human)
11 case-control (human)
6 animal experimental studies

Risk of Bias

Case control
Selection & Exposure bias



Cross-sectional: fair quality

Animal studies : most have high risk of bias ➔ blinding & randomization process

Study Findings

Object	Human Study	Animal Study
Nerves	• Abnormal development of myenteric plexus (MP)[9,11] • Fewer & smaller ganglion cells[10,11,13] • Denser fibrillar network & larger surface ganglia[12] • ICC-IM higher in upper pouch, ICC-MY is absent. Immature in upper oesophageal of OA patients.[14] • Neuronal genes was seen but none for enteric nervous system[16]	**Oesophageal Pouch :** (+) galanin and S100 (-) anti-VIP, slight CGRP immunoreactivity[17,19] Sparse myenteric ganglia[22] **TOF** : (-) anti-VIP[22] **Generally** : Deficient extrinsic nerve fiber plexus[18,22] & abnormal distribution of nerve tissue[19]
Epithelial	• Mucous glands arranged in clusters or abnormally high[5,6] • Stratified squamous & some pseudostratified epithelium[6,16] • Hyperplastic lining epithelium[13]	**TOF** : Pseudostratified columnar epithelium[20]
Muscle & Cartilage	• Cartilage was seen[5,6,7] • Not well organized[5,6,13,15] & higher mean muscular surface[12] • Slender & loose, endoplasmic reticulum swollen, granulated>clear vesicle[11] • Smooth muscle gene is overexpressed in TOF[16]	
IHC Expression	**Oesophageal Pouch :** (-) : GDNF[10], anti-SY[10] (+) : S100[10,13] **TOF :** (-) : NSE[11,13], SP[11], Nkx2.1[16] (+) : Anti-P[13], VIP[11],NOS[11] ➔ especially in myenteric ganglia **General :** (-) : anti-NF[10,13], TGF-b[15], BMP Ligand & type 1-receptor[9,16] (+) : BMPRI[9,16], SOX2[16]	

Key Findings

- **Disturbance in signalling** molecule may cause dysmotility.[16,9]
- Defects in neurons (e.g. no ganglia, thickened nerve fibers) ➔ **undeveloped myenteric plexus**[8,10,11,13,14]
- **Abnormality in organelles** might cause disturbance in motor function (e.g. swollen mitochondria, imbalance of vesicles, neurotransmitter)[11]

Conclusion

- Disruption in the intrinsic nervous system & abnormality in myenteric plexus may contribute to dysmotility.
- Need to be interpreted with care due to high risk bias of studies.