Mini-symposium: Esophageal Atresia and Tracheoesophageal Fistula

Motility, digestive and nutritional problems in Esophageal Atresia

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EDUCATIONAL AIMS

The reader will come to appreciate that:

- Digestive and nutritional problems are frequent and interlinked in esophageal atresia.
- A multidisciplinary approach is needed in esophageal atresia.
- Esophageal atresia is not only a surgical neonatal problem but has lifelong consequences for digestive and nutritional morbidity.

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SUMMARY

Esophageal atresia (EA) with or without tracheoesophageal fistula (TEF) is a rare congenital malformation [1,2]. The live-birth prevalence of EA is 1.8 per 10 000 births in France [3]. The prognosis of EA has benefited from advances in medical care, including neonatal and surgical procedures, and has therefore improved significantly over the past three decades. Its survival rate now exceeds 95% and an increasing number of patients reach adulthood [2,3]. However, digestive/nutritional problems remain frequent in this population both in early infancy and at long-term follow-up [4].

WHY ARE DIGESTIVE, MOTILITY AND NUTRITIONAL PROBLEMS A CONCERN IN PATIENTS WITH EA?

Gastro-esophageal reflux (GER)

Patients with EA are at major risk of having GER [5]. Several factors contribute to the physiopathology of GER in EA (Table 1).

Anastomotic stricture

An anastomotic stricture [AS] may arise because of important anastomotic tension related to a long-gap between the two esophageal pouches, occurrence of a post-operative anastomotic leak and GER [18].

Dysmotility

Dysmotility is not only a consequence of surgical repair as abnormal innervation is present at birth. It involves the Auerbach plexus, ganglion cells, interstitial cells of Cajal (ICC), and both excitatory and inhibitory intramural nerves mostly in the distal esophageal segment rather than in the proximal esophagus [19–22]. Dysmotility is explained by an imbalance of neurotransmitter excretion in nerve cells with decreased expression of neuronal markers, including vasoactive intestinal polypeptide (VIP) and nitric oxide synthase (NOS) [19,20]. These congenital changes in the innervation may lead to abnormal contraction and relaxation and subsequent dysphagia, GER, and feeding difficulty in children with EA [23].

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Nutritional problems

Dysphagia is one of the main causes of nutritional problems. Causes of dysphagia include esophagitis, GER, eosinophilic esophagitis, dysmotility, anastomotic strictures, esophageal outlet obstruction, aspiration and fear of feeding. Predictors of poor oral intake are long gap atresia, CHARGE association, and neurologic abnormalities [24]. GER and esophagitis have been implicated as causes of feeding difficulties. However, motility abnormalities may contribute to a much greater extent to dysphagia. Anastomotic strictures are another frequent cause of dysphagia and feeding difficulties.

Fundoplication, which can create a functional esophageal outlet obstruction in the context of dysmotility, may also cause or aggravate dysphagia and feeding difficulties. This is supported by a study of children receiving a fundoplication, where 4.3% of the cohort without EA presented with dysphagia, versus 17% in children with EA [25].

Aspiration is an under-recognized cause of feeding difficulty in children with EA. Any respiratory symptom during feeding, including tachypnea, wheezing, and cough may compromise feeding especially in infants [26–28].

Finally, EA patients may develop a fear of eating or texture aversions related to a history of food impaction [29].

All these mechanisms are often associated and contribute to reduced energy intake which leads to under-nutrition and growth failure.

The Prevalence and How to Explore Digestive, Motility and Nutritional Problems in Patients with EA (Table 2)

GER

GER is frequent in patients with EA, especially in isolated forms, where it is reported in almost all the patients and often requires fundoplication [30]. Depending on age, patient selection and diagnostic methods, the prevalence of GER in patients with EA varies from 20% to 63% [4,6,10,17,31–45]. GER can persist lifelong. Complications such as late or recurrent anastomotic stenosis, esophagitis and Barrett’s Esophagus (BE) can be observed during childhood, adolescence and adulthood (Table 3). There are few longitudinal studies of the natural history of Gastro-esophageal Reflux in the EA population, and as a result the risk of recurrence of GER has not been accurately assessed. GER appears to be particularly frequent during the first months of life, but especially within the first 5 years in type C EA patients [the most common type of TEF]. Koivusalo longitudinally assessed GER with esophageal pH-metry and histology in 61 children and showed that the prevalence of GER increased gradually from 16% at age 6 months to 51% at age of 5 years, while 44% of children still had GER at the age of 10 years [41]. Nonetheless, after 3 years of age, new cases of GER are rare and most of the patients presenting with GER are symptomatic [41].

24 hour esophageal pH-metry remains the gold standard for the diagnosis of GER [46]. Koivusalo et al. suggested that early esophageal pH-metry (i.e. before the age of 6 months) has a good specificity and positive predictive value for the outcome of EA associated GER but is not a good predictor of unfavorable GER or need for anti-reflux surgery [38]. Specific normal values for esophageal pH-metry are not available in EA patients, but reflux index, total number of reflux periods with pH<4 and numbers of periods of pH<4 lasting more than 5 minutes are very similar in EA patients to those in normal infants of the same age [47,48]. A systematic esophageal pH-metry screening for GER by 9–12 months of age is recommended.

Esophageal pH-impedance monitoring is a more recent technique that presents advantages compared to isolated esophageal pH-metry. It allows the evaluation of retrograde bolus movements in the esophagus independent of the pH, identifying non acidic reflux also in the postprandial period and in patients receiving acid-suppressing therapy. It is a dynamic technique and, therefore, can detect the direction of the flow, so that reflux can be distinguished from swallowed oropharyngeal contents. Moreover, it can accurately determine the height of the reflux and reflux-related symptoms. Combined with pH monitoring, it can distinguish between acidic and non-acidic reflux episodes [10]. However, the technique still has limitations: high cost, limited added value regarding therapeutic implications, and lack of evidence-based parameters for the assessment of gastroesophageal reflux and symptom association in children [49]. Experience of esophageal pH-impedancemetry is increasing in EA patients [9,10,17,44,50,51] and has demonstrated that reflux events are mainly non acidic (62.7% of reflux episodes), and that mean acid clearing time and mean bolus clearing time were significantly longer in EA patients.
compared to controls, adding to the understanding of the pathophysiology of GER in this population [9,10,50]. On rare occasions, such as in infants presenting with dying/cyanotic spells or those found to have a direct time-related event with non-acidic reflux (using a score), pH-impedancemetry can be helpful when considering the indication for fundoplication. Thus, it is a convenient technique in research for the evaluation of new drugs and for the study of swallowing abnormalities [9,10,51].

There are no studies assessing the benefit of routine upper gastrointestinal endoscopy in the follow-up of patients with EA. Eighty percent of grade C or D EA patients present with either moderate or severe esophagitis or gastric metaplasia at any time in follow-up, but the risk of occurrence is maximal during the first 3 years of life. The risk of having unfavorable history after 6 years of repeated normal biopsies is very low [42,43]. Endoscopic esophageal mucosal abnormalities can be observed in patients with EA despite the absence of symptoms.

When performed, upper gastrointestinal endoscopy should carefully examine the upper part of the esophagus (inlet patch is more frequent in this population [52]), esogastric junction and anastomosis area. In addition, the endoscopist should look for stenosis, a diverticulum or fistula, hiatal hernia, and peptic or eosinophilic esophagitis. In any case, when an endoscopy is performed and even when it appears macroscopically normal, at least 4 biopsies, in quadrants, one centimeter above the Z line and one biopsy in the middle part of the esophagus are recommended for Barrett and eosinophilic esophagitis screening. The number of biopsies should be increased in the presence of macroscopic abnormalities. GER can remain asymptomatic, and several studies have shown the absence of correlation between clinical signs and complications of GER (mainly esophagitis) in this population [17,35,36,42,43].

In children who underwent a fundoplication, repeated systematic endoscopy is recommended, as recurrence of GER and peptic esophagitis or Barrett’s Esophagus are possible for these patients [25,30,53].

**Anastomotic stricture**

AS is the most frequent post-operative complication occurring in 18% to 60% of patients with EA [18,54–57]. Clinical signs include dysphagia, vomiting, cough, recurrent respiratory infections and poor weight gain [56,58]. A history of an esophageal foreign body in a young child with EA [usually retained food such as chicken] is highly suggestive of an AS.

AS is diagnosed by a contrast X-ray or endoscopy. Although no consensus definition of AS exists, it is defined by a reduction of esophageal diameter compared to an age-related normal esophagus with associated symptoms. Stricture index (SI) can be calculated with the formula SI= (D-d)/D, in which “D” is the largest diameter of the esophagus closed from the stricture and “d” is the stricture diameter. SI has been used to assess the degree of the stricture at contrast X-Ray [59,60] or at endoscopy [61]. Routine screening for anastomotic stenosis has been advocated by some authors starting 1 month after surgery [59,62], while the majority recommend to wait for clinical signs suggestive of esophageal stenosis [54,56,57].

**Dysmotility**

Dysphagia is a common occurrence in 22–48% of older children and adults with EA [11,36,63]. Esophageal motility can be assessed by a contrast study, esophageal manometry (water perfused or more recently high resolution) or video manometry. All studies suggested one can ascertain the degree of dysmotility; rating it as mild, moderate or severe esophageal dysmotility [64]. With manometry, the patterns of esophageal dysmotility include 3 types: pressurization 15%, distal contraction 50% and aperistalsis 35%. Consistently, the pattern of esophageal dysmotility is not predictive of the presence or severity of dysphagia [65] nor the outcome of fundoplication. There is currently no evidence for the benefit of using esophageal manometry to direct medical management.

An upper gastrointestinal contrast study is predictive of delayed esophageal emptying and dysmotility. When performed, an upper gastrointestinal contrast series allows for early detection of dysmotility, and can differentiate degrees of severity [31].

**Nutritional problems**

The reported rates of feeding abnormalities varies from 6% to 11% [24,29,66]. After solid food introduction in the diet, the following food difficulties have been observed: slow to feed (52%), cough or choking with feeds (32%), vomiting with feeds (16%) [67], food refusal (16%) or dysphagia (61%) [4]. Children with EA have a significant reduction of height and weight (mean height z score -1.78±1.7) and mean weight for height (-1.1±0.9). Only 7% of patients with EA are less than the 5th percentile for height and weight and low birth weight is predictor of a smaller size [37].

Initial evaluation of dysphagia includes an endoscopy to evaluate the anastomotic site and esophageal inflammation contributing to symptoms. There is a poor correlation with the symptom of dysphagia and inflammation. It has been reported that 38% of patients with normal esophageal biopsies have food impactions and only 32% of patients with endoscopic inflammation have food impactions [42].

**TREATMENT AND FOLLOW-UP**

**Gastro-esophageal Reflux**

GER is frequent during infancy and complications due to GER are observed mostly during the first 2 years of life [42]. Most of the complications due to GER in EA are linked to acid reflux (ie esophagitis, refused to eat, anastomotic stenosis) rather than non-acidic reflux. Medical management of GER by whatever the agent used (mainly proton pump inhibitor (PPI) and H2 receptor antagonists) is successful by reducing gastro-intestinal symptoms, respiratory symptoms or showing an improved weight gain [68]. There are no efficient pro-kinetics currently available.

There is no evidence to justify increasing systematically the dosage of PPI in EA: neither evidence of abnormal high acidic secretion in this condition, nor resistance to PPI reported.

Esophageitis seems more frequent in EA patients and is the leading cause of Barrett’s Esophagus, which is a premalignant lesion that can be prevented by PPI [69]. Long-term treatment with PPI might expose the patient to adverse events although this has been poorly studied in children. Long term PPI treatment is not generally recommended in the pediatric population. Therefore, the

<table>
<thead>
<tr>
<th>Time of occurrence</th>
<th>Complication</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short term</td>
<td>Laryngomalacia aggravation</td>
<td>18-60%</td>
</tr>
<tr>
<td></td>
<td>Anastomotic stenosis</td>
<td>9-53%</td>
</tr>
<tr>
<td></td>
<td>Peptic esophagitis</td>
<td>6-11%</td>
</tr>
<tr>
<td>Middle term</td>
<td>Recurrent anastomotic stenosis</td>
<td>6%</td>
</tr>
<tr>
<td>Long term</td>
<td>Bronchial hyperreactivity</td>
<td>5-36%</td>
</tr>
<tr>
<td></td>
<td>Barrett esophagus</td>
<td>(3 cases reported)</td>
</tr>
</tbody>
</table>
benefit/risk of long term PPI treatment should be balanced in this population and the need for prolonged treatment reaccessed on a regular basis.

Indications for fundoplication vary widely from one center to another. Cumulative risk to have a fundoplication performed in EA patients is up to 45%. In the literature, indications may include failure of maximum conservative therapy for GER and/or esophagitis, an apparent life-threatening event, recurrent anastomotic stenosis, fistula recanalization and failure to thrive [37,68,70]. In long gap EA, GER seems particularly frequent and is associated with a higher risk of anastomotic stenosis, suggesting that fundoplication should be proposed for a large proportion of those children. The timing of fundoplication varies from one center to another but is often performed during early childhood, between 1 and 24 months after the atresia repair [70]. However, performing a fundoplication early in life exposes the child to a higher risk of failure [71].

In highly selected cases, when severe reflux persists despite fundoplication, or after repair of a tracheoesophageal cleft, or in severe microgastric, total gastric dissociation could be considered [72]. However, long term complications including dumping syndrome, nutritional deficiency and growth failure, long term dependency to enteral feeding, Barrett’s Esophagus and esophago-jejunal anastomosis stenosis have been recently reported [73,74].

Due to the high frequency of GER in infancy and risk of complications, there is a general recommendation to systematically treat all EA patients with PPI during the first months of life. An esophageal pH-metry after stopping PPI is recommended at that time. Long-term regular endoscopic follow-up of EA patients is also recommended.

Anastomotic stricture

Conservative treatment consists of intraluminal dilations, to obtain a stable esophageal diameter that allows normal eating and disappearance of symptoms. Dilations can be done either using semi-rigid dilators (as Savary-Giliard bougies) or balloons. There is no consensus about the optimal diameter and frequency of the dilations [59,75]. Dilations sessions are usually repeated every 1 to 2 weeks until a stable diameter is obtained [59,75] or resolution of the symptoms is achieved [54,61]. Anastomotic stricture (AS) resection and re-anastomosis or partial or total esophageal substitution is reserved for conservative management failures.

Recurrent AS is defined as reappearance of symptoms, 3 or more times, more than 30 days after last dilation [75]. Experimental data as well as clinical experience suggest that GER is the major cause of recurrent anastomotic stenosis [76,77] and in these cases fundoplication has to be considered [18]. Recurrent AS can also be treated by steroid stricture injection [78–81], topical application of the anti-fibroblastic agent mitomycin C [82] (Figure 1) and stents [83–86].

Dysmotility

Intrinsic abnormal motility of the esophagus is a constant feature in EA where pro-kinetics are unlikely to be as efficient as in a child with normal esophageal motility [87]. Therefore, due to their potential side effects and lack of efficiency, the use of pro-kinetics is not recommended in EA patients. There is no current specific drug option to treat dysmotility.

Nutritional problems

Aggressive pulmonary toileting, early treatment of infections, and use of inhaled medications are all critical to maintain lung health and reduce the risk of feeding difficulties.

Careful nutritional follow-up is required and relies on growth and height charts. Several measures can be combined to prevent or treat under-nutrition: individually adapted food consistency and timing of introducing solid foods, oral rehabilitation with help of a speech therapist and psychologist, nutritional complements, even enteral nutrition via a gastrostomy or via a nasogastric tube.

Figure 1. Left: Recurrent anastomotic stenosis in a 15 months old patient with esophageal atresia (arrow) Right: Upper GI series 3 years after one application of mitomycine C showing the absence of stenosis.

SPECIAL FOCUS ON LONG GAP EA

Long-gap (LG) EA is a high-risk group for digestive and nutritional problems. LG represents 10% to 26% of the total esophageal atresia (EA) patients—according to its definition—mainly observed in type A (pure EA >50%) but also in other forms (type B, C and D). It is a major surgical challenge. Options for esophageal reconstruction include the use of native esophagus—which is the preferred strategy—or esophageal replacement with stomach, colon, or small intestine. Besides surgical difficulties, digestive and nutritional problems appear much more frequent than in other forms of EA and are responsible for a high morbidity. These problems result from the combination of several factors: EA per se (gastric and esophageal dysmotility, GER), anatomical form (microstomia), and surgery (lack of oral feeding due to delayed anastomosis, anastomotic tension, anastomotic stenosis, GER, consequences of esophageal replacement).

Several factors contribute to the physiopathology of GER in long gap EA. Excessive tension at the esophageal anastomosis is associated with a higher incidence of GER.

Compared to non-long gap population, the need of repeated dilations (up to 50%), fundoplication (20 to 44%, often performed very early in life), as well as gastrostomy (almost 100%), and malnutrition (33%) are much more frequent in long gap EA.

Microgastria, as severe, often observed on an additional challenging problem for gastrostomy feeding (feeding intolerance, leakage around the stoma, dumping syndrome) and need for fundoplication.

Although there are no randomized studies comparing esophageal end to end to anastomosis to gastro-coloplasty, and the published series are small and retrospective, it has been suggested a higher risk of recurrent esophageal stenosis in end to end anastomosis, similar rate of GER but more under-nutrition is observed in the long term following gastro-coloplasty. The long gap population is a small but high-risk group for prolonged digestive and nutritional problems. These patients require a prolonged multidisciplinary follow-up and should be referred to reference centers.

CONFLICTS OF INTEREST

None.

FUTURE DIRECTIONS FOR CLINICAL RESEARCH

To assess natural history of gastro-esophageal reflux with pH-impedancemetry.

To assess the incidence of Barrett esophagus and esophageal carcinoma in children and adults with esophageal atresia.

To assess the prognostic value of high definition manometry in esophageal atresia.

To test new prokinetics in the management of dysphagia.

References


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